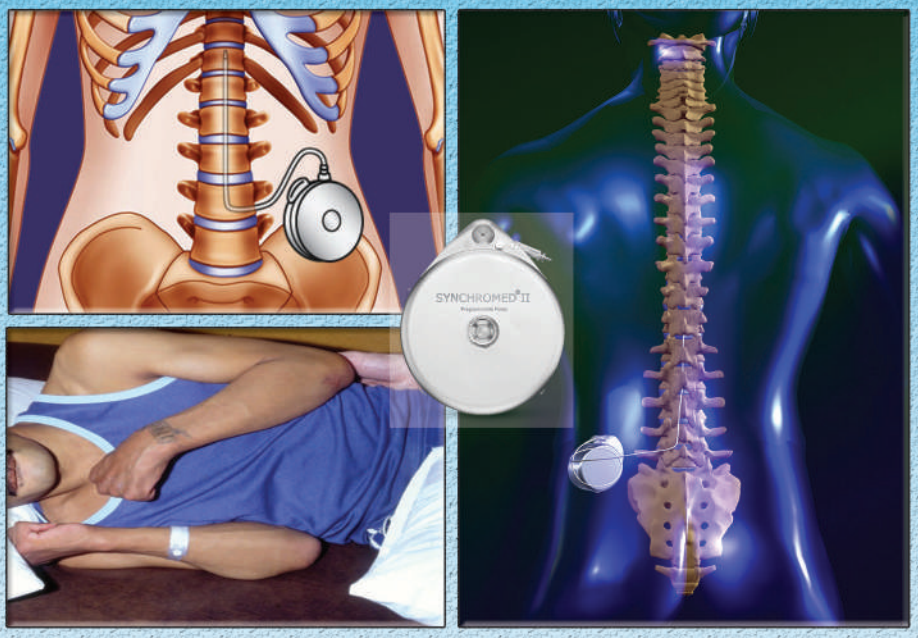
MOH/P/PAK/287.15(TR)

HEALTH TECHNOLOGY ASSESSMENT REPORT

MINISTRY OF HEALTH MALAYSIA

CONTINUOUS INTRATHECAL BACLOFEN (ITB) INFUSION FOR SEVERE SPASTICITY AND DYSTONIA



MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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Health Technology Assessment Report

CONTINUOUS INTRATHECAL BACLOFEN (ITB) INFUSION FOR SEVERE SPASTICITY & DYSTONIA

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

Please contact: htamalaysia@moh.gov.my, if you would like further information.

Published by
Malaysian Health Technology Assessment Section, (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Complex E, Precinct 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 603 88831246
Fax: 603 8883 1230

ISBN: 978-967-0769-11-0

Available on the MOH website:
http://www.moh.gov.my/v/hta

This HTA report was issued in December 2014.

AUTHORS

Dr. Junainah Sabirin
(Public Health Physician)
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Madam Sin Lian Thye
Nursing Officer / Information Specialist
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Nur Farhana Mohamad
Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXPERT COMMITTEE

Dr. Ooi Ai Lee
Rehabilitation Physician and
Head of Department of Rehabilitative Medicine
Hospital Raja Permaisuri Bainun, Ipoh

Dr. Ng Kee Hong
Rehabilitation Physician
Hospital Raja Permaisuri Bainun, Ipoh

Dr. Kavitha Uma Ratnalingam
Rehabilitation Physician
Hospital Sungai Buloh

Dr. Chern Phei Ming
Rehabilitation Physician
Hospital Rehabilitasi Cheras

Dr. Maslina Yazid
Rehabilitation Physician
Rehabilitative Medicine Department
Hospital Tengku Ampuan Rahimah Klang

Dr. Cheang Chee Keong
Consultant Neurosurgeon and
Head of Department of Neurosurgery
Hospital Raja Permaisuri Bainun, Ipoh

Dr. Alex Khoo Peng Chuan
Paediatric Neurologist
Hospital Raja Permaisuri Bainun, Ipoh

EXPERT COMMITTEE (CONTD...)

Dr. Kavita Bhojwani
Consultant Anaesthetist and
Head of Department of Anaesthesiology
Hospital Raja Permaisuri Bainun, Ipoh

Dr. Siti Aminah Akhbar Merican
Family Medicine Specialist
Klinik Kesihatan Seberang Takir
Terengganu

Dr. Liew Boon Seng
Neurosurgeon
Neurosurgery Department
Hospital Sungai Buloh

Dr. Noor Azman bin A. Rahman @ Mohd
Neurosurgeon
Neurosurgery Department
Hospital Sultanah Aminah
Johor Bharu

Dr. Irene Looi
Consultant Neurologist
Hospital Seberang Jaya, Pulau Pinang

YBhg. Datin Dr. Rugayah Bakri
(Public Health Physician)
Deputy Director
Head, Health Technology Assessment Section
(MaHTAS),
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS

YBhg. Dato' Dr. Md. Hanip bin Rafia
Consultant Neurologist and
Head of Department of Neurology
Hospital Kuala Lumpur
(Head of Neurology Services, Ministry of Health)

YBhg. Datuk Mr. Johari Siregar bin Adnan
Consultant Neurosurgeon and
Head of Department of Neurosurgery
Hospital Sultanah Aminah, Johor Bahru
(Head of Neurosurgery Services, Ministry of Health)

Dr. Yusniza Mohd. Yusof
Rehabilitation Physician
Hospital Rehabilitasi Cheras
(Head of Rehabilitation Services, Ministry of Health)

Dr. Khoo Teik Beng
Consultant Paedictric Neurologist
Paediatric Institute
Hospital Kuala Lumpur

YBhg. Associate Professor Dr. Mazlina Mazlan
Consultant Rehabilitation Physician
Department of Rehabilitation Medicine
Faculty of Medicine, University Malaya
University Malaya Medical Centre

ACKNOWLEDGEMENT

The authors for this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.

DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Background

Spasticity is a common problem in many conditions that affect motor function, among them stroke, traumatic brain injury (TBI), spinal cord injury (SCI), multiple sclerosis (MS), and cerebral palsy (CP). Severe, uncontrolled spasticity can make transfers, sitting, and hygiene difficult or impossible, impairing ambulation and self care in patients. Spasticity can cause pain, decreased range of motion, gait problems, contractures, fractures, decubitus ulcers, and pressure sores, which, in turn, lead to decreased independence, functioning, and quality of life. Dystonia has been classified as primary, primary plus, secondary, and heredo-degenerative. Secondary dystonia is perhaps the most common type due to its association with two frequent conditions: CP and TBI. Secondary dystonia is typically generalised and causes progressive disability, discomfort, and deformity.

The control of spasticity and dystonia progresses from less to more invasive treatments. Oral baclofen results in virtually undetectable levels of the drug in the spinal cord (its site of action), whereas intrathecally administered baclofen at 1/100th the dose results in cerebrospinal fluid levels comparable to serum levels following oral medications. Moreover, oral doses are associated with side-effects such as sedation, behavioural changes, confusion, ataxia, urinary frequency and insomnia. Hence, intrathecal delivery methods have been developed as an alternative to chronic systemic administration in an attempt to reduce pharmacological side effects such as physical tolerance, psychological dependency, and neurotoxicity. Intrathecal delivery of baclofen has been used to control spasticity in cases in which oral medications have failed to bring about the expected results. Unsuccessful treatment of spasticity and dystonia affects not only the patient, but also the caregivers, and increases the overall cost of the medical care. Continuous intrathecal baclofen (ITB) infusion has not been practised in any government hospitals in Malaysia. Therefore, there is a need to assess the feasibility of using continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions who were uncontrolled by conventional treatment. This Health Technology Assessment (HTA) was requested by Rehabilitation Physicians, Hospital Raja Permaisuri Bainun, Ipoh, Perak.

Technical features

Lioresal intrathecal (baclofen injection) is a muscle relaxant and antispastic. Its chemical name is 4-amino-3 (4-cholophenyl) butanoic acid. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyic (GABA), and may exert its effect by stimulation of the $GABA_B$ receptor subtype. Lioresal intrathecal when introduced directly into the intrathecal space permits effective cerebrospinal fluid (CSF) concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration. Lioresal intrathecal is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the United States Food and Drug Administration (U.S. FDA) specifically for the administration of Lioresal intrathecal into the intrathecal space. The implantable pump that administers the medication can be programmable or non programmable, depending on the type of medication delivery required. Programmable pumps are for flexible medication delivery as dose titration and regulation will vary and non-programmable pumps are for fixed rate medication delivery when dosage requirement is expected to be stable. Careful selection and screening of patients prior to initiation of ITB therapy for reduction of spasticity and spasms is crucial to achieving successful outcomes. Regardless of the cause of spasticity, implantation of a pump for ITB therapy must be preceded by a successful test trial to ensure for adequate response to medication.

Policy question

In Ministry of Health facilities, should continuous ITB infusion be used for treatment of patients with severe spasticity or severe dystonia or having both conditions who were uncontrolled by conventional treatment?

Objectives

1. To assess the safety of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.
2. To assess the effectiveness of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.
3. To assess the economic implications of using continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.
4. To assess the organizational issues related to the use of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to June 2014), EBM Reviews-Cochrane Central Register of Controlled Trials (July 2014), EBM Reviews – Database of Abstracts of Review of Effects (3rd Quarter 2014), EBM Reviews-Health Technology Assessment (3rd Quarter 2014), EBM Reviews-NHS Economic Evaluation Database (3rd Quarter 2014). Parallel searches were run in PubMed. No limits were applied to the search. The last search was run on 27 June 2014. Additional articles were identified from reviewing the references of retrieved articles. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results

A total of 918 titles were identified through Ovid interface, Pubmed and references of retrieved articles. A total of 372 abstracts were screened using the inclusion and exclusion criteria. After reading, appraising and applying the inclusion and exclusion criteria to 111 full text articles, 76 full text articles comprising of six randomised controlled trials (RCTs), two prospective follow-up studies of RCTs, 51 pre- and post-intervention studies, 13 observational studies (case-control, cohort, cross sectional), and four cost-effectiveness analysis / cost-utility analysis were finally included for this review.

A. SPASTICITY

Sixty three articles (studies) related to the effectiveness, safety and cost-effectiveness of continuous ITB infusion for treatment of patients with severe spasticity were included in this review. The total pooled sample size of the included studies was 3,754 and the length of follow-up ranged from three months to 156 months.

Effectiveness:

- The mean Ashworth Scale (AS) scores significantly reduced from 2.8 – 4.6 at baseline (before treatment) to 0.4 – 2.6 at follow-up (post implantation).
- Reduction of the mean AS scores in the upper extremities was of slightly lesser magnitude compared to lower extremities. The mean Spasm Frequency Score (SFS) significantly reduced from 1.8 – 3.6 at baseline to 0.4 - 1.5 at follow-up.
- Significant reduction in Reflex Score (RS) for the affected lower limbs.
- Significant reduction in pain was reported in 10 studies.
- Improved functional status as evidence by objective measurement and subjective measurement:
  - Improvement in ease of care and individual problems, caregiver assistance, nursing care, self care, gross motor function, activities of daily living (bathing, grooming, dressing, mobility, facilitation of transfer), independence, gait and ambulation, participation in daily activities and upper limb function.
- Changes in disability, and handicap were inconclusive.
- Significant improvement in quality of life which include improvement in bodily pain and discomfort, parental impact time, mental health, physical health, sleep and rest, mobility, body care, recreation and past time, and psychosocial.
- Four studies reported significant improvement in quality of sleep.
- Seventy one percent to 80% of treatment goals were fully attained.
- Satisfaction with continuous ITB infusion treatment was reported by 82% to 90.5% of patients and caregivers.
- One study reported reduction of 2.7 hospital days per patient in the first year post implantation compared with the year prior to implantation.
- Hip subluxation / dislocation:
  - In patients with CP overall, 90.9% of hip manifested no deterioration or had improvement of their migration percentage class during the year of ITB.
  - No significant difference in the rate of secondary hip reconstructive surgery between non ambulatory CP patients who underwent selective dorsal rhizotomy (SDR) or continuous ITB infusion (reconstruction was required in 25% to 32% of hips despite spasticity intervention with either procedure).
  - No significant difference in the rate of dislocation (10.6% in SDR group) versus (7.4% in continuous ITB infusion group).
- The 8-year survival in non-ITB cohort was 88% and in the ITB cohort was 92%, P = 0.073.

Safety:

- Complication rates vary between studies.
- Complications were either drug or device related (surgical procedure or system related; catheter or pump).
- Complications reported ranged from mild to severe.
- There were no deaths related to continuous ITB infusion.
- Drug related adverse events:
  - Most frequent reported include hypotonia, somnolence, headache, nausea, vomiting, dizziness, seizures, constipation, bradycardia, and urinary retention.
  - Complications were often transient and reversible.
  - Drug tolerance occurred in 1.7% to 22% of patients and was managed with 'drug holiday'.
  - Baclofen overdose occurred in 1.0% to 11.1% of patients.
  - Frequency of delirium was 9.5% (12/126 patients) whereby 66.6% were due to intoxication and 33.3% were due to withdrawal.
  - ITB may impact sexual functions. However, the effects seemed to be reversible.
- Device related adverse events:
  - Surgical procedure related adverse events frequently reported were pocket seroma, pocket infection, CSF leak, surgical wound infection, and programming errors.
  - Several technical issues related to catheter and pump were reported (catheter break, catheter kink, catheter dislodged, catheter occlusion, catheter ruptured, catheter migration, back pain at catheter site, and pump malfunction).
  - Complications can usually be easily corrected surgically. However, some required explantation or replacement of the device.
  - Significantly higher incidence of deep infections in paediatric group (10%) than in adult group (0%), $P = 0.028$.
  - The presence of percutaneous endoscopic gastrostomy (PEG) tube increased the incidence of infection, $P = 0.008$.
  - Progression of scoliosis after continuous ITB infusion was inconclusive.

Cost-effectiveness analysis / cost-utility analysis:

- Four studies conducted in the Netherlands, United States of America (U.S.A.), France, and Japan reported that continuous ITB infusion for treatment of patients with severe spasticity seemed to be cost-effective based on the willingness to pay threshold for each country.

Daily dosing

- The average daily dose of baclofen to achieve reduction range from 205.3 µg/day to 591.5 µg/day at the most recent follow-up.

B. DYSTONIA

Six articles (studies) related to the effectiveness and safety of continuous ITB infusion for treatment of patients with severe dystonia were included in this review. The total pooled sample size of the included studies was 163 and the length of follow-up ranged from six months to 64 months. There was no retrievable evidence on the cost-effectiveness of continuous ITB infusion for treatment of patients with severe dystonia.

Effectiveness:

- Significant reduction in dystonia based on measurement using the Barry-Albright Scale (BAD) and Burke-Fahn-Marsden (BFM) rating scale.
- Improved functional status which includes improvement in upper limbs function, patient management, posture control, nursing care, and ease of care.
- Seventy nine percent of patients were satisfied with the implant.

Safety:

- Few complications or adverse events were reported.
- There were no deaths related to continuous ITB infusion.
- The reported drug related adverse events were constipation, loss of bowel and bladder control, decreased neck / trunk control, drowsiness, overdose or withdrawal.
- Baclofen overdose occurred in 7.1% to 16.0% of patients.
- Catheter fracture, catheter rupture, CSF leak, wound breakdown, wound dehiscence, alarm failure, infection, skin erosion were the commonly reported device related adverse events.

C. SPASTICITY AND / OR DYSTONIA

Seven articles (studies) related to the effectiveness and safety of continuous ITB infusion for the treatment of patients with severe spasticity and / or dystonia were included in this review. The total pooled sample size of the included studies was 297 and the length of follow-up ranged from one month to 118 months. There was no retrievable evidence on the cost-effectiveness of continuous ITB infusion for treatment of patients with severe spasticity and / or dystonia.

Effectiveness:

- Significant reduction in spasticity was reported in five studies.
- Significant reduction in dystonia was reported in two studies.
- Reduction in resting metabolic rate after continuous ITB infusion.
- Improved functional status which includes improvement in gross motor function, transfer, patient care management, seating position, endurance, and walking.
- Goal attainment:
  - Significant increase in satisfaction and performance domains of the Canadian Occupational Performance Measure (COPM).
  - Using the goal attainment scaling (GAS) scale, 70% of subjects attained their goals.

Safety:

- There were no deaths related to continuous ITB infusion.
- Most of the complications reported were device related adverse events such as catheter displacement, catheter fracture, CSF leak, or infection.
- Complication rate was higher in children with dystonia (0.71 complications per subject year of follow-up) compared with those with spasticity (0.25 complications per subject year of follow-up), $P = 0.0017$.
- Greater rate of curve (Cobb's angle) progression in patients with pumps inserted before the age of 15 years (before growth spurt).

Organizational

- Effective treatment of spasticity and dystonia involved multidisciplinary team. The team should be trained in ITB therapy. Management of patients with baclofen pumps by experienced teams will help minimise serious complications. Patient and caregiver indicated that they would have benefited from additional education about the pump and its ongoing maintenance.
- The cost of Synchromed II pump per unit is RM 36,000.00. The pump last for four to seven years depending on the flow rate. The estimated average cost per treated patient per annum (drugs, pump and refill kit) range from RM 15,715.00 to RM 37,080.00 over life span of the pump.

Conclusion

There was substantial fair level of retrievable evidence to suggest that continuous ITB infusion was effective in reducing spasticity, reducing pain, improved function and quality of life in patients with severe spasticity who were unresponsive or cannot tolerate oral baclofen. Majority of the treatment goals were attained. Patients and caregivers were satisfied with the treatment. Although there was the risk of adverse events related to continuous ITB infusion, the treatment is considered relatively safe, minimally invasive and reversible. Continuous ITB infusion for treatment of patients with severe spasticity seemed to be cost-effective in some countries.

There was limited fair level of retrievable evidence to suggest that continuous ITB infusion was also safe and effective in reducing dystonia, reducing spasticity, improved function and quality of life in patients with severe dystonia or having both spasticity and dystonia who were unresponsive or cannot tolerate oral baclofen. Complication rates were higher in children with dystonia compared with those having spasticity. There was no retrievable evidence on the cost-effectiveness of continuous ITB infusion for treatment of patients with severe dystonia or having both spasticity and dystonia.

This treatment system requires long term monitoring by an experienced healthcare team. Besides proper training for the healthcare teams, patients and caregivers education has been critical in avoiding severe consequences of ITB withdrawal. Despite the large upfront cost for the procedure, the long-term effects can be potentially money saving.

Recommendation

Continuous ITB infusion may be utilised in patients with severe spasticity or severe dystonia or having both conditions who are unresponsive or cannot tolerate oral baclofen, by trained multidisciplinary healthcare teams. Criteria for patient selection should be developed. Records of patients on continuous ITB infusion should be maintained by the treating physicians. Patient's outcome research is warranted on a long term basis.

TABLE OF CONTENTS

ABBREVIATIONS

ITB	Intrathecal Baclofen
SCI	Spinal Cord Injury
MS	Multiple Sclerosis
TBI	Traumatic Brain Injury
CP	Cerebral Palsy
SDR	Selective Dorsal Rhizotomy
CSF	Cerebrospinal fluid
U.S. FDA	United States Food and Drug Administration
U.S.A.	United States of America
RCT	Randomised controlled trial
AS	Ashworth Scale
MAS	Modified Ashworth Scale
SFS	Spasm Frequency Score
RS	Reflex Score
VAS	Visual Analogue Scale
GMFM	Gross Motor Function Measure
PEDI	Paediatric Evaluation of Disability Inventory
FIM	Functional Independence Measure
FAQ	Functional Assessment Questionnaire
BIS	Barthel Index Score
GGI	Gillette Gait Index
EDSS	Expanded Disability Status Scale
AI	Ambulation Index
DRS	Disability Rating Scale
ISS	Incapacity Status Scale
SIP	Sickness Impact Profile
HSCL	Hopkins Symptoms Checklist
CHQ-PF50	Health Questionnaire-Parent Form 50
SSQL	Stroke-Specific Quality of Life Scale
MSWS-12	12 –item MS Walking Scale
BAD	Barry-Albright Scale
BFM	Burke-Fahn-Marsden
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
GAS	Goal attainment scaling
COPM	Canadian Occupational Performance Measure
CI	Confidence interval
SD	Standard deviation
QALY	Quality adjusted life years

HEALTH TECHNOLOGY ASSESSMENT

1 BACKGROUND

Spasticity is a common problem in many conditions that affect motor function, among them stroke, brain injury, spinal cord injury (SCI), multiple sclerosis (MS), and cerebral palsy (CP).[1] Spasticity is defined as a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one of the component of upper motor neuron syndrome. Clinically, spasticity is a constellation of symptoms characterised by hypertonicity, hyperactive muscle stretch reflexes, and abnormal spinal reflexes. In some cases there also may be clonus and muscle spasms.[2] Spasticity may be evaluated using clinical scores, stretch monosynaptic reflexes, and polysynaptic flexion reflexes. Severe, uncontrolled spasticity can make transfers, sitting, and hygiene difficult or impossible, impairing ambulation and self care in patients. Spasticity can cause pain, decreased range of motion, gait problems, contractures, fractures, decubitus ulcers, and pressure sores, which, in turn, lead to decreased independence, functioning, and quality of life.[2] In a study conducted among 27 CP patients attending the Paediatric Rehabilitation Clinic at University of Malaya Medical Centre, 11.1% patients reported severely affected quality of life, 25.9% patients reported moderately affected quality of life and 37% reported mildly affected quality of life.[3] Dystonia has been classified as primary, primary plus, secondary, and heredo-degenerative. Secondary dystonia is perhaps the most common type due to its association with two frequent conditions: CP and traumatic brain injury (TBI). Secondary dystonia is typically generalised and causes progressive disability, discomfort, and deformity.[4]

In a systematic review and meta-analysis of 49 studies, Oskoui et al. reported that the pooled overall prevalence of CP was 2.11 per 1,000 live births [95% confidence interval (CI):1.98 to 2.25].[5] Among 900 children with disability attending rehabilitation services provided by primary health care clinics in four states in Malaysia, 22% were having CP.[6] Similarly, in another study involving 168 disabled children, 28.6% were having CP.[7] In Malaysia, the estimated prevalence of MS is 1 to 2 per 100,000 population.[8,9] The incidence of spinal injuries in Malaysia is on the rise following similar trend of rapid development and increasing number of building constructions sites, and motor vehicles.[10] A retrospective study conducted in the Spinal unit, Department of Orthopaedics and Traumatology, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) found that motor vehicle accidents were identified as the leading cause of SCI (39%) and of the complications cited, bladder and bowel problems were the most frequent (65%), followed by spasticity (27.3%) and pressure ulcer (26%).[11]

Management of motor disorders is typically comprehensive and multidisciplinary, including physiotherapy, occupational and speech therapy, orthotics, device-assisted modalities, pharmacologic intervention, and orthopaedic and neurosurgical procedures.[12] Spasticity is not always detrimental. A weak flaccid limb can interfere with some daily activities such as transfer, dressing, grooming and perineal care. Spasticity provides posture and tone to a limb that can assist with weight bearing even if the patient cannot walk. However, excessive increase in tone may interfere with these activities. Thus, it is only when spasticity interferes with function or puts the individual at risk of hurting himself or herself that it needs to be treated.[13]

Control of spasticity and dystonia progresses from less to more invasive treatments.[2] The usual approach to treating spasticity relies on trying to decrease muscle tone with physical and occupational therapy, braces, and serial casting. Oral medications are important in the treatment of generalised spasticity. The medications commonly used are baclofen (Lioresal), dantrolene (Dantrium), tizanidine (Zanaflex) and gabapentin (Neurotin). Injections of phenol or botulinum toxin type A has been used for treatment of focal spasticity.[13] These conservative treatments are not always sufficient; ≈ 30% of patients with spinal origin spasticity are not effectively treated with oral medications.[2] Oral baclofen has been used since 1970s. In the 1980s, lumbar intrathecal administration of baclofen was pioneered by Penn and Kroin in individuals with spasticity of spinal origin. Oral baclofen results in virtually undetectable levels of the drug in the spinal cord (its site of action), whereas intrathecally administered baclofen at 1/100th the dose results in cerebrospinal fluid levels comparable to serum levels following oral medications.[1] Moreover, oral doses are associated with side-effects such as sedation, behavioural changes, confusion, ataxia, urinary frequency and insomnia.[12] Hence, intrathecal delivery methods have been developed as an alternative to chronic systemic administration in an attempt to reduce pharmacological side effects such as physical tolerance, psychological dependency, and neurotoxicity.[14] Intrathecal delivery of baclofen has been used to control spasticity in cases in which oral medications have failed to bring about the expected results.[13] Intrathecal baclofen (ITB) is variously referred to as intrathecally-administered baclofen, intrathecal baclofen infusion, and continuous baclofen infusion.[1] Surgical treatment of spasticity tends to be reserved for the most refractory cases. It includes myelotomy, cordotomy, cordectomy, lengthening, releasing or transferring a tendon, osteotomies and selective dorsal rhizotomy (SDR).[13]

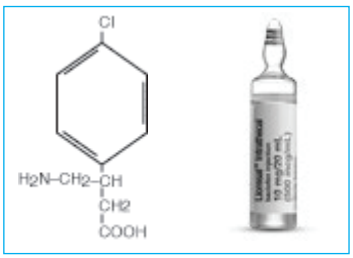
Oral medications used to treat dystonia include baclofen, clonazepam, trihexyphenidyl, and levo-dopa. In general, oral medications diminish dystonia in minority of participants and cause dramatic improvement in even fewer. The use of ITB for dsytonia was reported in 1991.[4] Unsuccessful treatment of spasticity and dystonia affects not only the patient, but also the caregivers, and increases the overall cost of the medical care. Patients experience pain, limitation in mobility and function, impaired social and professional activities, a decrease in the perception of overall quality of life, and in some cases, depression. Caregivers experience greater difficulty with procedures, such as urinary catheterisation, and an increased demand for nursing and providing assistance in activities of daily living. The overall cost of medical care increases because of the need to treat symptoms, such as fractures, dislocations, and decubitus ulcers, which develop secondary to the spasticity.[2]

Continuous ITB infusion has not been practised in any government hospitals in Malaysia. Therefore, there is a need to assess the feasibility of using continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions who were uncontrolled by conventional treatment. The goals of treatment are to decrease spasticity, reduce pain, improve ease of care, improve comfort and positioning, increase independence, prevention of further contractures, and improve quality of life.[2] This HTA was requested by Rehabilitation Physicians, Hospital Raja Permaisuri Bainun, Ipoh, Perak.

2 TECHNICAL FEATURES

2.1. LIORESAL® INTRATHECAL (baclofen injection)[15]

LIORESAL INTRATHECAL (baclofen injection) is a muscle relaxant and antispastic. Its chemical name is 4-amino-3(4-cholophenyl) butanoic acid and its structural formula is:



It is a sterile, pyrogen-free, isotonic solution free of antioxidants, preservatives or other potentially neurotoxic additives indicated only for intrathecal administration. The drug is stable in solution at 37°C and compatible with cerebrospinal fluid (CSF). Each millilitre of LIORESAL INTRATHECAL contains baclofen U.S.P. 50 mcg, 500 mcg or 2000 mcg and sodium chloride in Water for injection; pH range is 5.0 – 7.0. Each ampoule is intended for single use only.

Clinical Pharmocology[15]

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyic (GABA), and may exert its effect by stimulation of the $GABA_B$ receptor subtype. LIORESAL INTRATHECAL when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration.

Pharmacodynamics / Pharmacokinetics of LIORESAL INTRATHECAL

Intrathecal bolus	
Adults Patients	• The onset of action is generally one-half hour to one hour after an intrathecal bolus. • Peak spasmolytic effect is seen at approximately four hours after dosing and effects may last for four to eight hours. • Onset, peak response, and duration of action may vary with individual patients depending on the dose and severity of symptoms.
Paediatric Patients	• The onset, peak response and duration of action is similar to those seen in adults patients.
Elimination clearance from the CSF	• 30 mL / hour
Continuous infusion	
Adults Patients	• LIORESAL INTRATHECAL antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. • Maximum activity is observed in 24 to 48 hours.
Paediatric Patients	• No additional information is available for paediatric patients.
Elimination clearance from the CSF	• 30 mL / hour

Indications

- LIORESAL INTRATHECAL is indicated for use in the management of severe spasticity.
- Patients should first respond to a screening dose of ITB prior to consideration for long term infusion via an implantable pump.
- For spasticity of spinal origin, chronic infusion of LIORESAL INTRATHECAL via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable CNS side effects at effective doses.
- Patients with spasticity due to TBI should wait at least one year after the injury before consideration of long term ITB therapy.
- LIORESAL INTRATHECAL is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the United States of America Food and Drug Administration (U.S.FDA) specifically for the administration of LIORESAL INTRATHECAL into the intrathecal space.

Contraindications

- Hypersensitivity to baclofen.

Precautions

- Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion.
- Safety and effectiveness in paediatric patients below the age of four has not been established.
- Patients should be infection free prior to screening and pump implantation.

2.2. Intrathecal Baclofen Pump Infusion

The method of drug delivery into the spinal canal is via a catheter that is attached to the pump device. There is a range of totally implanted catheters with implanted reservoirs and manual pumps as well as totally implanted catheters with implanted infusion pump. The implantable pump that administers the medication can be programmable or non programmable, depending on the type of medication delivery required. Programmable pumps are for flexible medication delivery as dose titration and regulation will vary and non-programmable pumps are for fixed rate medication delivery when dosage is expected to be stable.[14]

An example of a flexible medication delivery pump is the SynchroMed electronic pump, manufactured by Medtronic Inc. (Minneapolis, MN, U.S.A.). This pump contains a collapsible reservoir that be filled with 10 to 18 ml of liquid medication, and a peristaltic pump that pushes medication through a bacteriostatic filter and catheter into the spinal canal. The design facilitates flexible dosing options and precise dose titration over time.

An example of a fixed rate pump is the Infusaid Infusion pump, manufactured by Arrow International, Reading, PA, U.S.A. One chamber holds the medication and the other, a charging fluid. Once inserted into the abdomen, the pump increases in temperature to body temperature, leading to expansion of the charging fluid, which pressurises the top chamber to push medication through the catheter.[14]

Patient selection and Evaluation[2]

Careful selection and screening of patients prior to initiation of ITB therapy for reduction of spasticity and spasms is crucial to achieving successful outcomes. Example of patient selection criteria used for spinal origin spasticity:

- Known chronic, stable, disease state - most often MS, spinal trauma, paralysis or paraplegic patients
- Severe, disabling spasticity (Ashworth score ≥ 3) interfering with mobility, activities of daily life, and / or nursing care
- Spasticity refractory to oral drug treatment and / or drugs not tolerated
- Painful spasms
- Positive evaluation by a multidisciplinary health care team
- Ability to provide informed consent and follow-through necessary to maintain implanted pump; and
- Positive response to ITB test (50 µg to 100 µg)

Goal Setting and Patient Education[2]

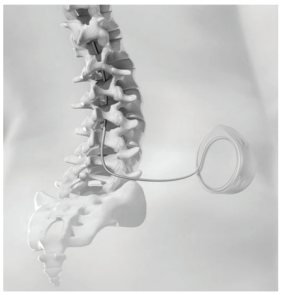
The patient, family, and caregivers must be counselled regarding realistic functional, nursing, and long-term care goals.

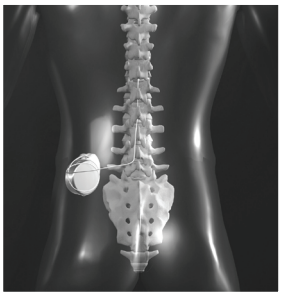
Intrathecal Baclofen Screening Test[2]

Regardless of the cause of spasticity, implantation of a pump for ITB therapy must be preceded by a successful test to screen for adequate response to medication. A common standard procedure is as follows: a patient receives a test bolus of 25 to 50 µg ITB via a lumbar puncture. In the absence of a positive response, indicated by a two-point reduction in Ashworth score four to eight hour following drug administration, the bolus dose is increased in a 25 µg increments up to maximum bolus of 100 µg. No more than one bolus is given in any 24 hour period. Once a positive response is observed without accompanying unacceptable loss of function, the patient is considered to be a candidate for pump implantation. In some cases the patient is evaluated further by continuous infusion. To do this, the screening dose is doubled or tripled, then delivered daily by continuous infusion for up to a seven day period.

Device Implantation and Maintenance[2]

Patients should be free of infection prior to implantation of the pump. The pump placement site should be evaluated and marked prior to surgery, taking into account the patient's physical characteristics and condition. The pump is implanted, using either local (spinal), or, more often general anaesthesia. The catheter is inserted into the lower lumbar area and positioned so that the tip is located in the region of T-10 to T-12. The catheter is introduced by a Touhy needle and sutured with an anchor to the fascia to avoid dislocation. Special sleeves or fixation pieces are provided with most catheter sets to avoid kinking at the site of maximal mechanical stress, at the lumbar entry through the subcutaneous tissue. The catheter is tunnelled anteriorly to the abdomen, where it is connected to the pump. The pump is inserted into a subcutaneous pocket located in the lower abdomen. Baclofen remains stable in the pump for at least 11 weeks. The pump is generally refilled every four to 11 weeks. Since sudden withdrawal of baclofen produces adverse effects in the patient, it is important to schedule pump refills well in advance of emptying the pump reservoir.[2]





During the postsurgical period, the site of implantation should be kept clean, dry, and protected from external pressure. Patients prone to CSF leaks should be medically managed to reduce leak occurrence. Once muscle tone has been decreased by ITB treatment, it is possible to begin to capitalise on physical therapy which helps to provide relief from contractures while increasing functioning and mobility. Physical therapy should be initiated as soon as possible after surgery and be continued in specialised rehabilitation institutions.[2]

Dosing

Typically, the initial starting dose after implantation is double the effective screening dose. The dose is titrated for maximum effect over the first 60 days after implantation. No increase in dose takes place in the first 24 hour after implantation. Beginning on Day two, the dose is increased daily by 10% to 30 % in adult patients, or 5% to 15% in paediatric patients, until the desired effect is achieved. The most useful criteria for dose adjustment is the effective suppression of reflexes and the decrease in muscle tone. Response to dose adjustment should become apparent ≈ five to six hour post-procedure. Once the effective dose has been ascertained and stabilized, the administration of the drug can be fine-tuned. Approximately 75% of patients require gradual dose increases over time in order to maintain the desired effect, especially in the six to 12 months following pump implantation. A sudden need for increased medication suggests a catheter complication such as leakage, occlusion, or repositioning, or pump malfunction. Other potential causes for varying medication requirements include acquired tolerance to the drug; diffusion or flow barriers, such as fibrosis; changes in the underlying disease; or the development of concomitant disease.[2]

3 POLICY QUESTION

In Ministry of health facilities, should continuous ITB infusion be used for treatment of patients with severe spasticity or dystonia or having both conditions who were uncontrolled by conventional treatment?

4 OBJECTIVES

4.1 To assess the safety of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.

4.2 To assess the effectiveness of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.

4.3 To assess the economic implications of using continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.

4.4 To assess the organizational issues related to the use of continuous ITB infusion for treatment of patients with severe spasticity or severe dystonia or having both conditions compared with conventional treatment.

Research questions

i. How safe is continuous ITB infusion compared with conventional treatment?

ii. What are the short and long term benefits of using continuous ITB infusion compared with conventional treatment for patients with severe spasticity or dystonia or having both conditions?

iii. What is the economic implication of using continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions?

iv. What are organizational issues related to the use of continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions?

5 METHODS

5.1. Literature search strategy

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to June 2014), EBM Reviews-Cochrane Central Register of Controlled Trials (July 2014), EBM Reviews – Database of Abstracts of Review of Effects (3rd Quarter 2014), EBM Reviews-Health Technology Assessment (3rd Quarter 2014), EBM Reviews-NHS Economic Evaluation Database (3rd Quarter 2014). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 27 June 2014. Additional articles were identified from reviewing the references of retrieved articles.

5.2. Study Selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1. Inclusion criteria

- Population: Patients with spasticity or dystonia or having both conditions (adult and children).
- Intervention: Continuous ITB infusion.
- Comparators: Conventional treatment (oral medication, injection of phenol or botulinum toxin type A, physical therapy, posterior dorsal rhizotomy) or placebo or no comparator.
- Outcome:
    i. Adverse events or complications – drug or device related
    ii. Severity of spasticity
    iii. Pain
    iv. Severity of dystonia
    v. Frequency and severity of spasm
    vi. Quality of life (patients and carers)
    vii. Functional outcome-mobility, activity of daily living, participation
    viii. Hospitalisation - admission, length of stay
    ix. Secondary complication due to spasticity (e.g. contraction, pressure ulcer)
    x. Economic evaluation
    xi. Organizational issues - operational, training, resources
- Study design: HTA report, Systematic Review, Randomised Controlled Trial (RCT), Non Randomised Controlled Trial, Pre- and Post-intervention study, Observational Studies (Cohort study, Case Control study, Cross Sectional study), and Cost-effectiveness / cost-utility analysis.
- Full text articles published in English.

5.2.2. Exclusion criteria:-

- Study design: Animal study, laboratory study, narrative review, case reports.
- Non English full text article.

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. Full text article was retrieved for those title and abstract considered as relevant and if it was unclear from the title and / or abstract whether the study was relevant or not. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3. Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool by two reviewers.[16] For SR the criteria assessed include selection of studies, assessment of quality of included studies, heterogeneity of included studies. For RCT, the criteria assessed were randomisation, allocation concealment, blinding, explanation on loss to follow-up, and intention to treat analysis. For cohort study, the criteria assessed were selection of the cohort, accurate measurement of exposure and outcome, confounding factors, follow-up adequacy and length. For case control study, the criteria assessed were selection of the cases and control, accurate measurement of exposure, and confounding factors. For economic evaluation, the criteria assessed include comprehensive description of competing alternatives, effectiveness established, effects of intervention identified, measured and valued appropriately, relevant resources and health outcome costs identified, measured in appropriate units and valued credibly, discounting, incremental analysis of the consequences and costs of alternative performed and sensitivity analysis performed. The Summary of CASP checklist is as in Appendix 4. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).[17]

5.4. Data extraction strategy

Data were extracted from the included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by another reviewer. Disagreements were resolved by discussion. Details on: (1) methods including study design, (2) study population characteristics including gender, age, cause of spasticity or dystonia, (3) type of intervention, (4) comparators, (5) type of outcome measures including: a) adverse events or complications related to the drug or pump, b) severity of spasticity, dystonia, pain, and frequency of spasm, c) quality of life, d) functional outcome, e) hospitalisation, f) secondary complication due to spasticity, f) economic evaluation, and g) organizational issues were extracted. The extracted data were presented and discussed with the expert committee.

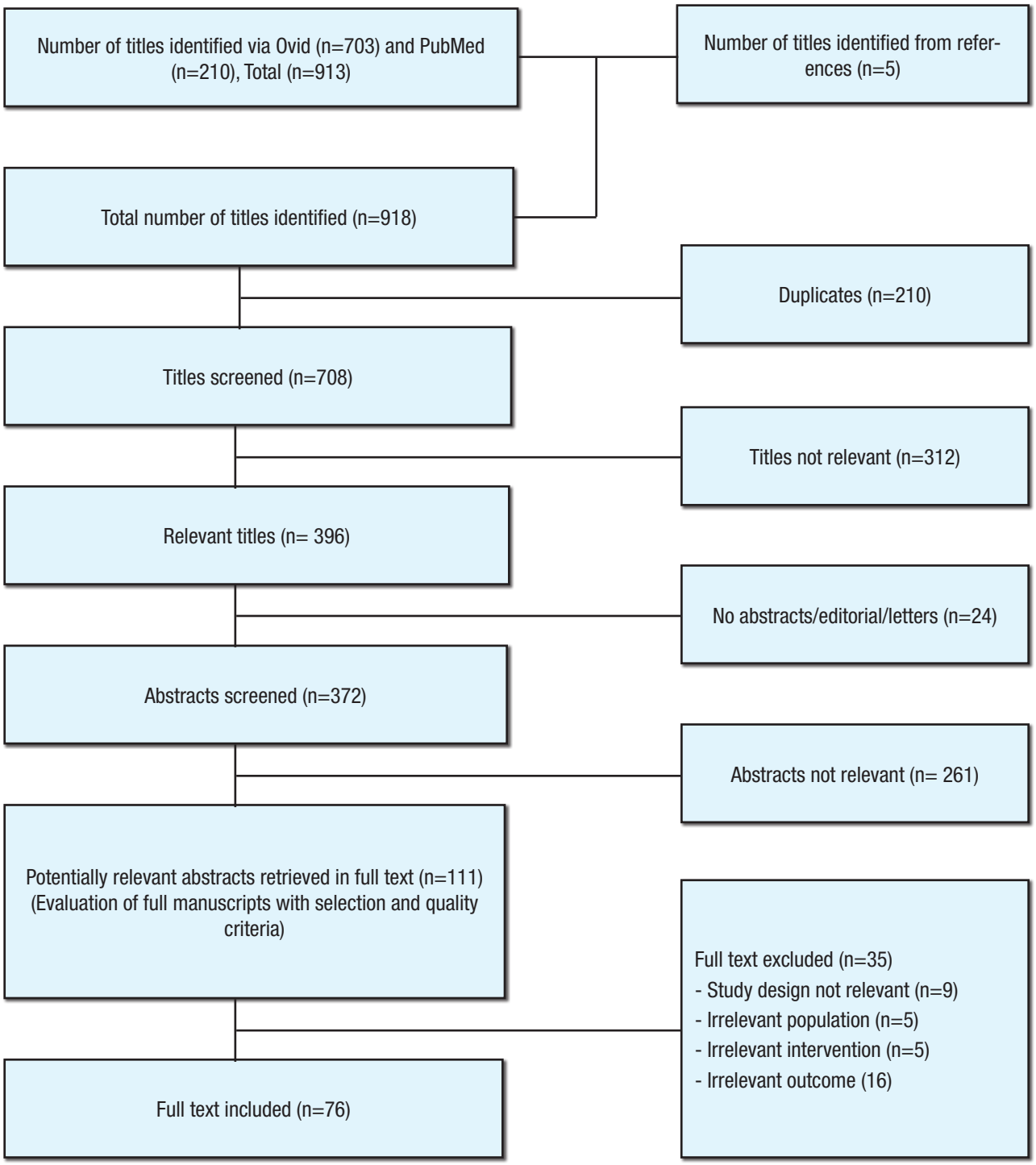
5.5. Methods of data synthesis

Data on the safety, efficacy and cost implication of using continuous ITB infusion for patients with spasticity or dystonia or having both conditions compared with conventional treatment were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6 RESULTS

A total of 913 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to June 2014), EBM Reviews-Cochrane Central Register of Controlled Trials (July 2014), EBM Reviews – Database of Abstracts of Review of Effects (3rd Quarter 2014), EBM Reviews-Health Technology Assessment (3rd Quarter 2014), EBM Reviews-NHS Economic Evaluation Database (3rd Quarter 2014), and PubMed. Five were identified from references of retrieved articles. After removal of 210 duplicates, 708 titles were screened. A total of 396 titles were found to be potentially relevant and 372 abstracts were screened using the inclusion and exclusion criteria. Of these, 261 abstracts were found to be irrelevant. One hundred and eleven potentially relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 111 full text articles, 76 full text articles were included and 35 full text articles were excluded. The articles were excluded due to irrelevant study design (n = 9), irrelevant population (n = 5), irrelevant intervention (n = 5), and irrelevant outcome (n = 16). The excluded articles are listed in Appendix 7. The 76 full text articles finally selected for this review comprised of six RCTs, two prospective follow-up studies of RCTs, 51 pre- and post-intervention studies, 13 observational studies (case-control, cohort, cross sectional), and four cost-effectiveness / cost-utility analysis. There was no HTA report on continuous ITB infusion for severe spasticity and dystonia.

FLOW CHART OF STUDY SELECTION



6.1. SPASTICITY

Sixty three articles (studies) related to the effectiveness, safety and cost-effectiveness of continuous ITB infusion for treatment of patients with severe spasticity met the inclusion criteria and included in this review. The included studies were: six RCTs [one compared ITB with standard treatment, one compared ITB with placebo for three months and followed by observational longitudinal study for one year, while in the other four studies each patient passed through two phases; (in phase 1, a screening dose was administered in a randomised, double blind, placebo-controlled fashion while phase 2 was open-label, long term, continuous infusion for patients with a positive response to the screening dose of baclofen injection)], two prospective follow-up studies of RCTs, 41 pre- and post-intervention studies, four cost-effectiveness / cost-utility analysis, and 10 observational studies. The articles were published between 1988 and 2013. The studies were conducted in the U.S.A., Netherland, Belgium, Italy, Turkey, Norway, Greece, Germany, United Kingdom, France, and Japan. The total pooled sample size of all included studies was 3,754 subjects. Samples sizes of each of the RCTs and the pre- and post-intervention studies ranged from six to 250, while the sample sizes for each of the observational studies ranged from 12 to 708. The length of follow-up ranged from three months to 156 months. Most of the study participants were non ambulant patients and three studies were conducted among ambulant patients. Most of the participants included in the studies had insufficient response to maximum doses of oral antispasmodic or had intolerable side effects and had Ashworth Scale scores of ≥ 3 in the lower extremities. The common causes of spasticity were CP, MS, TBI, SCI, and stroke.

Risk of bias

In five of the RCTs, the method of allocation concealment was unclear and there was no blinding in one of the RCT. The pre- and post-intervention studies have clear and consistent inclusion and exclusion criteria in subject selection. Cross sectional studies have potentially higher risk of bias. The results are summarised in Table 1.

Table 1. Assessment of risk of bias of RCT

Criteria assessed Study	Randomisation (sequence generation)	Allocation concealment	Blinding	Intention to treat analysis	Explanation Loss to follow-up
Hoving et al.[18]	Yes	Yes	No	Yes	Yes
Gilmartin et al.[20]	Yes	Can't tell	Yes	Yes	Yes
Van Schaeybroecket al.[22]	Yes	Can't tell	Yes	Yes	Yes
Meythaler et al.[23]	Yes	Can't tell	Yes	Yes	Yes
Meythaler et al.[24]	Yes	Can't tell	Yes	Yes	Yes
Middel et al.[25]	Yes	Can't tell	Yes	Yes	Yes

6.1.1. Effectiveness of continuous ITB infusion for treatment of patients with severe spasticity

Forty five articles (studies) related to the effectiveness of continuous ITB infusion for treatment of patients with severe spasticity was included in this review. Three primary outcome measures were used to evaluate spasticity: Ashworth Scale (AS) / Modified Ashworth Scale (MAS), Spasm Frequency Score (SFS), and Reflex Score (RS). The description of the rating scale is in Appendix 5. There were many objective outcome measures used to evaluate function such as Visual Analogue Scale (VAS), Gross Motor Function Measure (GMFM), Paediatric Evaluation of Disability Inventory (PEDI), Functional Independence Measure (FIM) for adults and WeeFIM for children, Gillette Functional Assessment Questionnaire (FAQ), Barthel Index Score (BIS), Gillette Gait Index (GGI), Melbourne Assessment for upper limb and Rankin scale. Disability measures include Expanded Disability Status Scale (EDSS), Ambulation Index (AI), Disability Rating Scale (DRS), and Incapacity Status Scale (ISS). Quality of life was measured using Sickness Impact Profile (SIP), Hopkins Symptoms Checklist (HSCL), Ferrans and Powers Quality of Life Index, Health Questionnaire-Parent Form 50 (CHQ-PF50), Stroke-Specific Quality of Life Scale (SSQL), and 12-Item MS Walking Scale (MSWS-12). Subjective improvement in function, quality of life, and degree of satisfaction were also reported.

a. Spasticity Outcome

Ashworth Scale (AS) / Modified Ashworth Scale (MAS)

The AS and MAS categorise the degree of increase in muscle tone (rigidity) during examination of the affected limb on a 5 or 6-points scale. Majority of the studies (34 out of 40 studies) measured the degree of rigidity using AS, only six used MAS.[18-57] Many studies demonstrated improvement in the muscle tone (rigidity). Thirty five studies reported a significant decreased in the AS scores or MAS scores at follow-up after treatment.[18, level I, 19, level II-2,20, level II-I, 21, level II-2, 22-25, level II-I, 26-57, level II-2] The mean AS scores reduced from 2.8 - 4.6 at baseline (before treatment) to 0.4 - 2.6 at follow-up (post implantation). The statistical significance was not reported in five studies.[20,28,41,45,55] Summary of the findings is shown in Table 2.

Twelve studies reported AS scores separately for upper and lower extremities (Table 3). Clinically significant relief of spasticity was demonstrated by reduction in the mean AS scores in the lower and upper extremities.[20, level II-I,23-24, level II-I,33, level II-2,35, level II-2,37, level II-2,49-51, level II-2] However, the reduction of the mean AS scores in the upper extremities was of slightly lesser magnitude compared to lower extremities. Three studies reported reduction in AS scores in ambulant children and adults with severe spasticity after treatment with continuous ITB infusion.[54-56, level II-2]

Table 2. Studies reporting spasticity outcome [muscle tone (rigidity)] after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Ashworth Scale Score		
			Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Middel et al. 1997[25]	N = 22 59% had MS, 41% SCI Mean age (SD): 48.3 (12.7) years	12 months	2.9 (0.5)	0.4 (0.5)	=0.002
Ordia et al. 1996[26]	N = 66 Spasticity of spinal cord origin Mean age: 42 years	Mean: 42 months (range, 23 to 70 months)	4.3	1.4	< 0.0005
Glugielmino et al. 2006[31]	N = 30 22 had MS, 1 lateral amyotrophic sclerosis, 3 spine lesions, 2 spine tumours, 1 spastic paraparesis, 1 other Mean age: 51±4.3 years	8 months	4.3 (0.6)	1.2 (0.3)	<0.0005
Boviatsis et al. 2005[34]	N = 22 15 had MS, 7 had SCI Average age: 44.7 years, range 27 to 63 years	Mean: 32 months (range, 9 to 55 months)	4.4 (MS group) 4.6 (SCI group)	2.1 2.6	<0.0001 =0.0134
Awaad et al. 2003[35]	N = 39 Children with CP Mean age (SD): 13.69 (7.43) years	18 months	3.3 (0.6)	1.6 (0.5)	<0.0005
Dario et al. 2001[38]	N = 20 13 had MS, 4 trauma, 2 spinal tumours, 1 spinal myelitis Mean age: 39.8 years	Mean: 22.4 months (range, 12 to 36 months)	4.4 (0.5)	1.8 (0.7)	<0.01
Becker et al. 1997[42]	N = 18 Had TBI or hypoxic brain injury Mean age:41 years, range 2.5 to 70 years	Range from 13 to 54 months	4.5	2.3	NA
Ochs et al. 1989[43]	N = 28 Chronic para-or tetraspasticity of various aetiologies Mean age (SD): 46 (12.2) years	24 months	3.6 (0.4)	1.8 (0.3)	NA
Gianino et al. 1998[52]	N = 25 Spasticity of spinal origin Mean age (SD): 39.4 (11.2) years	12 months	3.8 (0.8)	1.5	=0.00000014
Zahavi et al. 2004[53]	N = 21 Spasticity of spinal origin Mean age (SD): 54.6 (12.5) years	Mean: 84.9 months (range, 66 to 108 months)	2.8 (0.9)	0.9 (0.9)	=0.00

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; TBI, traumatic brain injury;SCI, spinal cord injury; NA, not available

Table 3. Studies reporting spasticity outcome [muscle tone (rigidity)] after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Ashworth Scale Score			
				Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Gilmartin et al. 2000[20]	N = 44 at baseline, N = 33 at 24 months post treatment Spastic CP Mean age: 10.3 years	24 months	LE UE	3.6 (0.6) 2.5 (1.9)	2.2 (0.8) 1.7 (0.7)	NA
Meythaler et al. 1999[23]	N = 6 3 had traumatic brain injury, 3 had unilateral stroke Average age: 50±8.9 years (SD)	3 months	LE UE	3.7 (1.0) 3.4 (0.9)	1.9 (0.6) 2.1 (0.9)	<0.0001 =0.0002
Meythaler et al. 2001[24]	N = 17 Adults with stroke Average age:50 years, range 16 to 86 years	12 months	LE UE	3.7 (1.0) 3.2 (1.1)	1.8 (1.1) 1.8 (0.9)	<0.0001 <0.0001
UCAR et al. 2011[29]	N = 30 18 had CP/ brain injury 12 had SCI Mean age:30.10±16.09 years	12 months	LE UE	3.8 (1.8) 2.2 (1.8)	1.7 (1.1) 1.1 (1.0)	<0.005 <0.005
Guillaume et al. 2005[33]	N = 129 30% MS, 26% SCI, 24% CP, 7% TBI, 2% Stroke, 11% others Mean age 35.2 ± 18.8 years	12 months	Cerebral origin LE UE Spinal origin LE UE	 4.0 (0.9) 3.6 (1.3) 3.7 (0.8) 1.7 (0.8)	 2.0 (0.8) 2.1 (0.9) 1.9 (0.8) 1.3 (0.5)	 <0.001 <0.001 <0.001 <0.001
Murphy et al. 2002[36]	N = 23 Children with CP Age ranged from 4.5 to 17.4 years	12 months	LE UE	3.3 (0.7) 2.7 (0.8)	2.4 (0.7) 2.1 (0.7)	≤0.01 ≤0.05
Dario et al. 2002[37]	N = 14 Adults with traumatic or anoxic acquired brain injuries Mean age: 38.8 years	Mean: 23.5 months	LE UE	4.3 (0.5) 4.1 (0.8)	2.7 (0.7) 2.3 (0.9)	<0.05 <0.05
Karenkov et al. 2002[39]	N = 12 Male patients with SCI	24 months	LE UE	4.2 2.2	2.2 1.0	<0.05 <0.05
Meythaler et al. 2001[41]	N = 13 Adolescents and adults with CP Average age:25 years, range 13 to 43 years	12 months	LE UE	3.4 (1.2) 3.0 (1.2)	1.5 (0.7) 1.7 (1.0)	<0.0001 <0.0001
Burns et al. 2001[51]	N = 14 Adults with spastic hypertonia in tetraplegia of spinal origin Age range from 25 to 64 years	12 months	LE UE	3.1 (1.3) 2.4 (1.1)	1.7 (0.0) 1.8 (1.0)	<0.0001 <0.0001
Mota et al. 2008[49]	N = 20 Children with spastic CP Age range from 5 to 15 years	12 months	UE	3.4 (0.7)	1.7 (0.7)	<0.05
Albright et al. 1995[50]	N = 38 Children with CP	12 months	UE	2.1 (0.8)	1.7	<0.001

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; TBI, traumatic brain injury, SCI, spinal cord injury; LE, lower extremity; UE, upper extremity; NA, not available

Spasm Frequency Score (SFS)

The SFS measures the number of sustained flexor and extensor muscle spasms in one hour on a 0 - 4 rating scale with 4 indicating > 10 spasms per hour. Seventeen studies reported on SFS. Table 4 and 5 summarises the results of spasm frequency outcome before and after treatment with continuous ITB infusion.

Table 4. Studies reporting spasticity outcome (spasm frequency) after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Spasm Frequency Score		
			Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Middel et al. 1997[25]	N = 22 59% had MS, 41% SCI Mean age (SD): 48.3 (12.7) years	12 months	2.2 (0.5)	0.6 (0.8)	=0.003
Ordia et al. 1996[26]	N = 66 Spasticity of spinal cord origin Mean age: 42 years	Mean: 42 months (range, 23 to 70 months)	3.6	0.5	< 0.0005
Natale et al. 2012[28]	N = 112 25 had MS, 21 CP, 10 TBI, 12 anoxic brain injury, 15 SCI, 7 familial paraparesis Average age: 43.2 years, range 7 to 63 years	Mean: 55 months (range, 12 to 72 months)	3.2 (0.4)	0.8 (0.2)	NA
Glugielmino et al. 2006[31]	N = 30 22 had MS, 1 lateral amyotrophic sclerosis, 3 spine lesions, 2 spine tumours, 1 spastic paraparesis, 1 other Mean age: 51±4.3 years	8 months	3.1 (1.1)	0.7 (0.4)	<0.0005
Guillaume et al. 2005[33]	N = 129 30% MS, 26% SCI, 24% CP, 7% TBI, 2% Stroke, 11% others Mean age: 35.2 ± 18.8 years	12 months	2.7 (1.2)	0.7 (1.0)	<0.001
Boviatsis et al. 2005[34]	N = 22 15 had MS, 7 had SCI Average age: 44.7 years, range 27 to 63 years	Mean: 32 months (range, 9 to 55 months)	3.3	1.5	<0.001
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Karenkov et al. 2002[39]	N = 12 Male patients with SCI	12 months	2.8	1.0	<0.05
Becker et al. 1997[42]	N = 18 Had traumatic brain injury or hypoxic brain injury Mean age: 41 years, range 2.5 to 70 years	Range from 13 to 54 months	2.2	0.9	NA
Gianino et al. 1998[52]	N = 25 Spasticity of spinal origin Mean age (SD): 39.4 (11.2) years	12 months	2.6 (1.2)	0.5 (0.8)	=0.000017
Zahavi et al. 2004[53]	N = 21 Spasticity of spinal origin Mean age (SD): 54.6 (12.5) years	Mean: 84.9 months (range, 66 to 108 months)	1.8 (0.6)	0.7 (1.1)	=0.001

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; TBI, traumatic brain injury, SCI, spinal cord injury; NA, not available

Ten studies reported statistically significant decreased in SFS.[25, level II-I, 26, level II-2, 31, level II-2, 33-34, level II-2,37-39, level II-2, 52-53, level II-2] Statistical significance was not reported in two studies.[28 level II-2, 48 level II-2] The mean SFS reduced from 1.8 - 3.6 at baseline (before treatment) to 0.4 - 1.5 at follow-up as shown in Table 4.

Meythaler et al. (1999, 2001, 2001), UCAR et al., and Burns et al. determined SFS for upper and lower extremities (Table 5).[23-24, level II-I, 29, level II-2, 41, level II-2, 51, level II-2] After treatment with continuous ITB infusion, SFS was decreased in the upper and lower extremities in all the studies. However, reduction was statistically significant in the studies by Ucar et al., and Burns et al. for the lower extremity and in the studies by UCAR et al., and Meythaler et al. for the upper extremity.

Table 5. Studies reporting spasticity outcome (spasm frequency) after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Ashworth Scale Score			
				Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Meythaler et al. 1999[23]	N = 6 3 had TBI, 3 had unilateral stroke Average age:50± 8.9 years (SD)	3 months	LE UE	1.3 (1.2) 0.8 (1.3)	0.8 (1.3) 0.0	=0.5 =0.1797
Meythaler et al. 2001[24]	N = 17 Adults with stroke Average age:50 years, range 16 to 86 years	12 months	LE UE	1.2 (1.3) 0.7 (1.0)	0.6 (1.0) 0.3 (0.8)	=0.4282 =0.8685
UCAR et al. 2011[29]	N = 30 18 had CP/ brain injury. 12 had SCI Mean age:30.10±16.09 years	12 months	LE UE	3.0 (1.8) 1.7 (1.8)	0.9 (1.0) 0.8 (0.9)	<0.001 <0.005
Meythaler et al. 2001[41]	N = 13 Adolescents and adults with CP Average age: 25 years, range 13 to 43 years	12 months	LE UE	1.4 (1.6) 1.2 (1.6)	0.6 (1.2) 0.2 (0.6)	<0.1024 <0.00135
Burns et al. 2001[51]	N = 14 Adults with spastic hypertonia in tetraplegia of spinal origin Age range from 25 to 64 years	12 months	LE UE	3.3 (0.9) 2.3 (1.6)	1.8 (1.5) 0.5 (0.9)	<0.0011 <0.2503

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; SCI, spinal cord injury; TBI, traumatic brain injury; LE, lower extremity; UE, upper extremity

Reflex Score (RS)

A 5-point scale documenting deep tendon reflexes was used at the biceps, patella and Archilles.[24, level II-I] Four studies used this assessment tool to examine changes in spasticity (Table 6).[24,34, 23-24, level II-I, 41, level II-2, 51, level II-2] The RS for the affected lower extremities decreased significantly in all the four studies. For the upper extremity, only the study by Meythaler et al. reported a significant reduction in RS from mean (SD) of 2.3 (0.7) to 0.5 (0.9) at 12 months, $P < 0.0001$.[41, level II-2]

Table 6. Studies reporting spasticity outcome (tendon reflex) after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after reatment	Ashworth Scale Score			
				Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Meythaler et al. 1999[23]	N = 6 3 had TBI, 3 had unilateral stroke Average age:50± 8.9 years (SD)	3 months	LE UE	1.8 (1.3) 2.3 (0.5)	0.5 (0.8) 1.7 (0.5)	=0.0208 =0.1088
Meythaler et al. 2001[24]	N = 17 Adults with stroke Average age:50 years, range 16 to 86 years	12 months	LE UE	2.4 (1.3) 2.4 (0.8)	1.0 (1.3) 1.5 (1.2)	<0.0001 =0.3337
Meythaler et al. 2001[41]	N = 13 Adolescents and adults with CP Average age:25 years, range 13 to 43 years	12 months	LE UE	2.5 (1.2) 2.3 (0.7)	0.7 (1.1) 0.5 (0.9)	<0.0001 <0.0001
Burns et al. 2001[51]	N = 14 Adults with spastic hypertonia in tetraplegia of spinal origin Age range from 25 to 64 years	12 months	LE UE	2.8 (1.3) 2.3 (0.2)	0.4 (0.9) 0.9 (0.2)	<0.0001 <0.2503

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; SCI, spinal cord injury; TBI, traumatic brain injury; LE, lower extremity; UE, upper extremity

b. Pain

Eleven studies reported on pain outcome after continuous ITB infusion in patients with severe spasticity.[18-19,25,29-31,33-34,38,45,55] Pain was mainly assessed using self reported VAS. Table 7 summarises the findings of six studies which reported significant reduction in pain after treatment with continuous ITB infusion.[18, level I, 19, level II-2, 25, level II-I, 29, level II-2, 31, level II-2, 38, level II-2] Significant reduction in pain was also reported in another four studies. Ramstad et al. in a pre- and post-intervention study involving 38 children with CP reported reduction in pain severity from median (range) of 2.0 (0 to 3) at baseline to 1.0 (0 to 3) at 18 months, P = 0.011.[30, level II-2] Guillaume et al. in a pre- and post-intervention study involving 129 patients reported that patients' pain assessments during follow-up showed significant reductions in pain (P < 0.001) after implantation in all 4 categories (worst pain, least pain, average pain, current pain) at all 4 visits.[33, level II-2] Similarly, Botviatsis et al. reported significant reduction in self reported visual analogue pain scale from 6.42/10 before treatment to 1.78/10, P = 0.0007 in 15 patients with MS.[34, level II-2] McClelland et al. reported statistically significant reduction of pain score (reduction of 54% from preoperative scores, P= 0.0082).[45, level II-2] In another pre- and post-intervention study involving 36 adult ambulatory patients with spasticity, Sadiq AS and Wang GC reported that continuous ITB infusion was beneficial in relieving pain in all 16 patients who had pain associated with spasticity.[55, level II-2]

Table 7. Studies reporting pain outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Type of pain score	Pain Score		
				Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Hoving et al. 2009[18]	N = 17 (9 in CITB Group, 8 in Control Group) Children with CP. Mean age (SD):13.2 (2.8 years)	6 months	0-10 VAS for pain. Higher VAS score represent less pain	CITB 2.4 (1.6) Control 3.7 (2.3)	6.6 (2.2) 2.4 (2.1)	4.2 (2.9) -1.3 (2.4) Differences between CITB and Control, P = 0.016
Hoving et al. 2009[19]	N = 17 children with CP	12 months	0-10 VAS for pain. Higher VAS score represent less pain.	CITB 2.4 (1.9)	7.8 (1.9)	5.4 (2.7) P = 0.002
Middel et al. 1997[25]	N = 22 59% had MS, 41% SCI Mean age (SD): 48.3 (12.7) years	12 months	0-10 self assessment scale for pain (0 was no pain, 10 was unbearable pain).	CITB 4.6 (3.2)	2.0 (3.0)	2.6 P=0.009
UCAR et al. 2011[29]	N = 30 18 had CP/ brain injury, 12 had SCI Mean age:30.10±16.09 years	12 months	0-10 self reported VAS for pain (0 was no pain, 10 was worst pain).	CITB 4.8 (4.2)	1.0 (1.4)	3.8 P<0.005
Glugielmino et al. 2006[31]	N = 30 22 had MS, 1 lateral amyotrophic sclerosis, 3 spine lesions, 2 spine tumours, 1 spastic paraparesis, 1 other Mean age:51±4.3 years	8 months	VAS scale for pain (0 was no pain, 10 was maximum pain).	CITB 6.2 (2.1)	3.3 (1.7)	2.9 P<0.005
Dario et al. 2001[38]	N = 20 13 had MS, 4 trauma, 2 spinal tumours, 1 spinal myelitis Mean age: 39.8 years	Mean: 22.4 months (range 12 to 36 months)	0-10 self reported pain score (0 was no pain, 10 was worst pain).	CITB 5.5 (2.2)	2.3 (1.9)	3.2 P<0.05

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; SCI, spinal cord injury; CITB, continuous intrathecal baclofen infusion group; VAS, visual analogue scale.

c. Functional Outcome

Twenty six studies reported on functional outcome such as motor function, ambulation, gait, mobility, functional skills, self care, caregiver assistance, social function, activities of daily living, and participation.[18-19,21,23-24,29-35,38,40-41,44,46-49,53-56,58] Table 8 to 11 summarises the findings of different measures of function.

Visual Analogue Scale (VAS)

Hoving et al. reported significant improvement in the 0-10 VAS for individually formulated problems and ease of care as shown in Table 8.[18, level I, 19, level II-2]

Table 8. Studies reporting functional outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity using VAS

Study	Patients	Length of follow-up after treatment	Type of pain score	Pain Score		
				Before ITB Mean (SD)	After ITB Mean (SD)	P Value
Hoving et al. 2009[18]	N = 17 (9 in CITB Group, 8 in Control Group) Children with CP. Mean age (SD):13.2 (2.8 years)	6 months	0-10 VAS. Score 0 very dissatisfied, score 10 very satisfied. VAS for individual problems.	CITB 2.2 (0.6) Control 2.3 (0.9)	6.3 (1.6) 2.2 (1.4)	4.0 (1.7) -0.2 (1.3) P = 0.001
			VAS for ease of care	CITB 2.7 (1.5) Control 1.5 (0.8)	6.6 (1.9) 1.6 (1.4)	3.9 (2.2) -1.3 (2.4) P = 0.016
Hoving et al. 2009[19]	N = 17 children with CP	12 months	0-10 VAS. Score 0 very dissatisfied, score 10 very satisfied. VAS for individual problems.	CITB 2.2 (1.1)	6.9 (1.8)	4.7 (2.0) P = 0.000
			VAS for ease of care	CITB 2.0 (1.0)	7.1 (2.0)	5.2 (2.1) P = 0.000

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; CITB, continuous intrathecal baclofen infusion group; VAS, visual analogue scale.

Paediatric Evaluation of Disability Inventory (PEDI)

Five studies used PEDI to assess functional outcome in children with CP. The PEDI assesses by interview the levels of caregiver assistance, functional skills, and modifications across the domain of self-care, mobility and social function.[40] PEDI measures the patient's functional capabilities for 197 items in the domains of mobility, self-care, and social function. Tasks are broken down into small steps, and patients ability to independently perform each subtask is documented as 1 if capable or 0 if not able to perform them independently. The tool also documents the amount of caregiver assistance required for various functional activities in these same domains of self-care, mobility, and social function.[35]

Table 9. Studies reporting functional outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity using PEDI

Study	Patients	Length of follow-up after treatment	Rating scale	Score		
				Before ITB Median (range)/ Mean (SD)	After ITB Median (range)/ Mean (SD)	Change from baseline P Value
Hoving et al. 2009[18]	N = 17 (9 in CITB Group, 8 in Control Group) Children with CP. Mean age (SD): 13.2 (2.8 years)	6 months	PEDI			
			PEDI functional skills	CITB 27.2 (13.9-64.1) Control 38.7(0.0-86.9)	27.2 (9.6-64.8) 37.4 (2.0-86.9)	0.0 (-7.4 to 5.7) 0.0 (-5.4 to -2.1), P = 0.663
			PEDI caregiver assistance	CITB 0.0 (0.0-61.3) Control19.0(0.0-00.0)	0.0 (0.0-65.4) 27.3 (0.0-84.0)	0.0 (-11.7 to 4.17) 0.0 (-16.0 to 16.0), P = 0.720
Hoving et al. 2009[19]	N = 17 children with CP.	12 months	PEDI			
			PEDI functional skills	CITB 32.9 (2.0-86.9)	38.8 (0.0-89.5)	0.0 (-15.0 to 15.8), P = 0.158
			PEDI caregiver assistance	CITB 0.0 (0.0-84.0)	0.0 (0.0-100.0)	0.0 (-16.6 to 26.3), P = 0.917
Ramstad et al. 2010[30]	N = 35 children with CP.	18 months	PEDI			
			PEDI functional skills: -Self care -Mobility -Social function	 CITB 33.6 (0.0-58.6) CITB 23.2 (0.0-53.1) CITB 57.9 (0.0-96.3)	 36.0 (0.0-73.6) 35.9 (0.0-54.8) 64.1 (0.0-100.0)	 P = 0.027 P = 0.017 P = 0.002
			PEDI caregiver assistance: -Self care -Mobility -Social function	 CITB 15.9 (0.0-57.9) CITB 11.7 (0.0-70.5) CITB 58.3 (0.0-100.0)	 11.6 (0.0-76.7) 36.9 (0.0-72.7) 65.9 (0.0-100.0)	 P = 0.272 P = 0.008 P = 0.004
Awaad et al. 2003[35]	N = 39 children with CP Mean age (SD): 13.69 (7.43) years	18 months	PEDI			
			PEDI functional skills: - Self care - Mobility - Social function	 CITB 34.2 (22.4) CITB 25.4 (20.4) CITB 44.9 (21.2)	 37.9 (29.0) 31.0 (24.6) 46.2 (26.6)	 P = 0.020 P = 0.023 P = 0.064
			PEDI caregiver assistance: - Self care - Mobility - Social function	 CITB 23.2 (30.9) CITB 17.5 (27.5) CITB 35.6 (35.7)	 29.7 (36.9) 30.7 (64.2) 39.9 (40.0)	 P = 0.501 P = 0.007 P = 0.105

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; CITB, continuous intrathecal baclofen infusion group; PEDI, Paediatric Evaluation Disability Inventory.

Hoving et al. in a RCT involving 17 children with CP reported PEDI caregiver assistance and functional skills did not differ significantly between the treatment and control group.[18, level I] They reported similar findings in a follow-up study of a RCT.[19, level II-2] In contrast, Ramstad et al. and Awaad et al. reported significant improvement in the PEDI functional skills and PEDI caregiver assistance in certain domains (Table 9).[30, 35, level II-2] Campbell et al. in a retrospective review of a pre- and post-intervention study in 21 children with intractable spasticity of cerebral origin reported that PEDI showed few functional changes in eight recipients with follow-up scores. In the PEDI mobility domain, two recipients improved in the care-assist dimension, and one recipient improved in the modifications dimension.[40, level II-2]

Gross Motor Function Measure (GMFM)

Four studies reported functional outcome using GMFM (Table 10). The GMFM is a standardised observational measure of gross motor function. The GMFM is a valid and reliable measure of independent mobility in children with CP. It provides a summary score and a score for each of five mobility dimensions: lying / rolling, sitting, crawling / kneeling, standing, and walking / running / jumping.[40]

The GMFM-66 significantly improved compared to the control group.[18, level I] Similarly, GMFM-66 showed significant improvement after treatment with continuous ITB infusion compared to before treatment.[19, level II-2, 30, level II-2] Hoving et al. reported significant improvement in GMFM-88 sitting and goal dimensions after treatment with continuous ITB infusion.[19, level II-2] Krach et al. reported significant improvement in all dimensions of GMFM-88 scores except for walking and running (Table 10).[21, level II-2]

Campbell et al. reported that the GMFM showed no functional change for most of the 17 recipients with baseline and follow-up scores. Two recipients showed functional improvements in the lying / rolling and sitting dimensions, and one of these improved in the crawling / kneeling dimension.[40, level II-2]

Table 10. Studies reporting functional outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity using GMFM

Study	Patients	Length of follow-up after treatment	Rating scale	Score		
				Before ITB Median (range)/ Mean (SD)	After ITB Median (range)/ Mean (SD)	Change from baseline P Value
Hoving et al. 2009[18]	N = 17 (9 in CITB Group, 8 in Control Group) Children with CP. Mean age (SD): 13.2 (2.8 years)	6 months	GMFM-66	CITB 20.0 (4.1) Control 32.9 (14.3)	21.3 (5.8) 31.3 (15.0)	1.2 (2.3) -1.6 (3.0), P = 0.028
			GMFM-88 lying and rolling	CITB 52.9 (14.0 - 90.0) Control 90.2 (22.0 - 96.0)	47.1 (18.0 - 82.0) 90.2 (18.0 - 96.0)	3.9 (-12.0 to 10.0) 0.0 (-10.0 to 0.0), P = 0.510
			GMFM-88 sitting	CITB 11.7 (0.0 - 17.0) Control 28.3 (2.0 - 78.0)	11.7 (2.0 - 23.0) 21.7 (8.0 - 78.0)	3.3 (0.0 to 10.0) 0.0 (-7.0 to 7.0), P = 0.085
			GMFM-88 goal dimensions	CITB 12.0 (0.0 - 35.0) Control19.3 (2.0 - 28.0)	15.0 (2.0 - 41.0) 17.8 (8.0 - 27.5)	3.3 (2.0 to 10.0) 1.3 (- 6.0 to 6.0), P = 0.140
Hoving et al. 2009[19]	N = 17 children with CP.	12 months	GMFM-66	CITB 24.7 (11.1)	26.1 (11.4)	1.4 (2.2), P= 0.034
			GMFM-88 lying and rolling	CITB 60.8 (14.0 - 96.0)	55.9 (18.0 - 96.0)	- 1.0 (- 25.0 to 11.0), P = 0.448
			GMFM-88 sitting	CITB 12.5 (0.0 - 78.0)	15.0 (0.0 - 95.0)	3.3 (- 4.0 to 22.0), P = 0.022
			GMFM-88 goal dimensions	CITB 17.0 (0.0 - 38.0)	17.0 (0.0 - 64.0)	4.0 (0.0 to 26.0), P = 0.007
Krach et al. 2005[21]	N = 31 children with CP. Mean age: 11.9 years	12 months	GMFM-88:			
			Lying	CITB 58.9 (37.8)	63.6 (33.9)	4.7 (8.9), P< 0.05
			Sitting	CITB 38.9 (37.1)	45.1 (39.0)	6.2 (9.9), P< 0.05
			Crawling	CITB 30.5 (38.3)	34.1 (43.2)	3.6 (8.0), P< 0.05
			Standing	CITB 14.2 (21.9)	20.8 (30.4)	6.5 (14.2), P< 0.05
			Walking & running	CITB 7.4 (13.1)	7.8 (14.5)	0.4 (3.2), NS
Ramstad et al. 2010[30]	N = 35 children with CP.	18 months	GMFM-66	CITB 22.7 (0.0 - 48.3)	24.0 (0.0 - 47.1)	P = 0.005

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; CITB, continuous intrathecal baclofen infusion group; GMFM, Gross Motor Function Measure; NS, Not significant.

Functional Independence Measure (FIM) / WeeFIM

Functional outcome was evaluated by using FIM / WeeFIM in few studies. FIM is a valid, standardised, reproducible, and universally accepted measure of function commonly used to track progress in rehabilitation. It assesses 18 items categorised into six motor and cognitive subscales (self-care, sphincter control, transfers, locomotion, communication, social cognition). A 7-point scale (1 [total assistance] to 7 [complete independence]) documents levels of independence in performing certain tasks with a maximum total core of 126.[47] The WeeFIM was used for children seven years and younger, and the FIM was used for all patients over seven years of age.[33]

Table 11. Studies reporting functional outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity using FIM/WeeFIM

Study	Patients	Length of follow-up after treatment	Rating scale	Score		
				Before ITB Median (range)/ Mean (SD)	After ITB Median (range)/ Mean (SD)	Change from baseline P Value
Guillaume et al. 2005[33]	N = 129 30% MS, 26% SCI, 24% CP, 7% TBI, 2% Stroke, 11% others. Mean age: 35.2 ± 18.8 years	12 months	FIM & WeeFIM: - Motor function - Cognitive function - Overall score	38.3 (25.1) 26.6 (11.3) 64.3 (34.0)	42.7 (27.7) 27.6 (10.4) 69.8 (36.0)	P<0.001 P<0.059 P<0.001
Dario et al. 2001[38]	N = 20 13 had MS, 4 trauma, 2 spinal tumours, 1 spinal myelitis Mean age: 39.8 years	Mean: 22.4 months (range 12 to 36 months)	FIM	33.8 (6.9)	58.7 (10.4)	P<0.05 In particular improvement regarded items: bathing, dressing the lower body and transferring of the body. Two patients were able to resume work.
Azouri et al.1996[44]	N = 18 Chronic para or tetraspasticity with various aetiologies. Average age (SD):38.5 (11.6) years.	Average: 37.4 months (range, 9 to 72 months)	FIM	39.9 (18.1)	58.5 (28.7) (At 6 months)	P<0.001 Improvement was statistically significant for all individual items, except for eating (most patients independent) and stair climbing (possible for only 2 patients).

Abbreviation: ITB, intrathecal baclofen; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; SCI, spinal cord injury; CITB, continuous intrathecal baclofen infusion group; FIM and WeeFIM

The improvement of FIM and WeeFIM scores was statistically significant for overall score, motor and cognitive function (Table 11).[33 level II-2] Dario et al. reported significant improvement in FIM score. In particular, the improvement regarded items such as bathing, dressing the lower body and transferring the body. Two patients in employment were able to resume work.[38, level II-2] In another study, Azouri et al. reported significant improvement in the average motor FIM score. The type and amount of improvement were however very different according to the nature and level of spinal cord lesion. Most dramatic improvements were observed in the 12 patients exhibiting a thoracic or low cervical lesion (average motor FIM score evolving from 50.9 ± 9.7 to 76.3 ± 15.5, Z = - 3.06, P < 0.01). Functional benefits were particularly marked for the following items, which gained two or more FIM scores in average: bathing, dressing lower body, and the three items related to transfers. In seven of these 12 patients, locomotion also improved. In five patients, walking ability improved (average initial FIM walking score: 3.6 ± 0.87, and 6-month score: 5.8 ± 0.2), and two of these patients acquired the ability to climb stairs. Functional improvement for the six most severely disabled patients, who were nearly totally dependent, was less obvious but still significant (average motor FIM score initially: 18 ± 6.6, at 6-month follow-up: 22.8 ± 6.7, Z = - 2.03, P < 0.05).[44, level II-2]

Significant improvement in FIM scores were also reported by Schiess et al., Ivanhoe et al., and Francisco GE and Boake C in studies involving post stroke spastic hypertonia patients.[46-48, level II-2]

Barthel Index Score (BIS)

Activities of daily living were measured using BIS. BIS is a scale that does not require the presence of a specialised physiotherapist or a rehabilitation physician. It ranges between 0 and 100 and is used as a record of what a patient is able to do, not of what he could do. It measures daily activities such as bathing, grooming, dressing and mobility and aims in establishing the patient's degree of independence from any help, physical or verbal. Scores near the middle categories, imply that the patient supplies over 50% of the effort to achieve a task. His performance should be established using the best available evidence. The usual source of information was an interview with the patient, his friends, relatives or caregiver, but sometimes direct observation is indicated.[34]

Ucar et al. reported significant improvement in BIS in a pre- and post-intervention study involving 30 patients with chronic, severe and generalised spasticity. Barthel index score increased from Mean ± SD of 38.70 ± 7.15 before treatment to 51.62 ± 14.69, $P < 0.005$. The most dramatic improvements of motor function were observed within the first year. Moreover, facilitation of transfer, active and passive physical therapy and nursing care were observed in all patients.[29, level II-2]

Similar findings was reported by Boviatsis et al. in 15 MS patients and seven SCI patients. In the SCI patients, preoperative average BIS were 17.1, ranging from 0 to 45 (median = 15). After the procedure, there was an overall functional status improvement expressed by a BIS increased to 50.7 ranging from 5 to 90 (median = 50), $P < 0.073$. Activities in which improvement reached statistical significance were dressing, $P = 0.04650$ and transfers, $P = 0.0016$. Post operatively, two became ambulatory with or without assistance, and two became wheelchair independent. They also reported improvement in transferring to or from the wheelchair, for dressing upper and lower body and toilet use with minor help or independently. Preoperative average BIS for the MS patients were 34.64, ranging from 10 to 65 (median = 35). After the procedure, there was an overall functional status improvement expressed by a BIS increased to 62.85 ranging from 10 to 95 (median = 65), $P < 0.022$. Amount of improvement was different for different activities. Activities that required reduction of spasticity at the lower limbs such as transfers, mobility and stair climbing showed statistically significant improvement ($P = 0.0018$, 0.0004, and 0.0011, respectively). Post operatively, three immobile patients became wheelchair independent, five could walk with help and four became independently ambulatory.[34, level II-2]

Gait and Ambulation Assessment

Three studies assessed the effect of continuous ITB infusion on gait parameters of ambulant patients.[54-56] Brochard et al. conducted a pre- and post-intervention study involving 21 ambulant children and young adults with CP. Functional walking status was assessed with part of the Gillette Functional Assessment Questionnaire. It is a validated 10-level functional measure of ambulation in the patient's own environment. They found that the Gillette Functional Assessment Questionnaire score increased significantly from Mean (SD) of 5.04 (SD, 2.08) to 6.09 (SD, 2.05), $P < 0.05$. Seven children were able to use less supportive walking aids. Four children abandoned their walkers: two for tripod crutches, one for two crutches, and one no longer used walking aid. After treatment, none of the children required walking aids that provided more support than those they previously used.[54, level II-2]

Similarly, in another study involving seven children with CP, Gillette Functional Assessment Questionnaire significantly improved from 6.10 (SD, 2.20) to 7.10 (SD, 2.00), $P = 0.02$. The Gillette Gait Index (GGI) which is a multivariate measure quantifying the degree of gait pathology and measures how closely an individual's gait pattern approaches typical gait improved from mean of 554.50 to 489.25, which was not significant although the improvement was large for three children. Parameters in the sagittal plane were significantly modified with a significant increased in step length from mean of 0.65 (SD, 0.25 m) to 0.74 m (SD, 0.25), $P< 0.05$.[56, level II-2] Sadiq SA, Wang GC reported the long-term ambulatory functions in 36 patients. Patients were followed from one to 13 years. They reported that all 36 patients retained ambulatory function.[55, level II-2]

Two studies assessed the effect of continuous ITB infusion on ambulation in poststroke spastic hypertonia patients.[46,48] Schiess et al. reported that gait performance improved after 12 months of ITB therapy when compared with baseline performance. Velocity at pre-implant was 0.55 ± 0.26 m/sec, compared with 0.77 ± 0.36 m/sec at 12 months post ITB, $P \leq 0.05$. Six-minute walk distance pre-implant was 558 ± 254 ft, compared with 746 ± 368 ft at 12 months post ITB, $P \leq 0.05$.[46, level II-2] Francisco et al. reported that walking speed increased by at least 1 cm/s in nine of 10 participants. The mean improvement in walking speed from baseline to post implantation was 15.4 ± 14.4 cm/s (range; 0.6 to 50.1 cm/s), $P = 0.051$. Mean walking speed increased to 52.0 ± 37.6 cm/s at follow-up from 36.6 ± 29.4 cm/s, at baseline. The effect size of the change in walking speed was 1.07, which is a large effect size.[48, level II-2]

Melbourne Assessment of Unilateral Upper Limb Function

Melbourne Assessment of Unilateral Upper Limb Function is an assessment protocol that measures the quality of upper limb function in children between the ages of five and 16 years with neurological impairment. The tool is composed of 16 items with a maximum score of 122. Motta et al. conducted a pre- and post-intervention study to evaluate the motor function of the upper limbs in 20 patients with CP treated with ITB.

They found that total average score for the dominant limb increased from a percentage value of 73.16% (SD, 14.4%) to a value at 12 months of 81.56 (SD, 12.34%). Five patients showed a score variation greater or equal to 12% (clinically significant). Total average score for the non dominant limb increased from a percentage value of 63.44% (SD, 22.5%) to a value at 12 months of 70.20% (SD, 21.59%). Three patients showed a score variation greater or equal to 12% (clinically significant). An analysis of total pre treatment and post treatment scores for range of movement, target accuracy, and fluency subskills showed statistically significant improvements ($P < 0.05$). A total of 25% of study population showed an improvement in quality of function of at least one limb.[49, level II-2]

Rankin Scale / Disability Ranking Scale (DRS) / Expanded Disability Status Scale (EDSS) / Incapacity Status Scale (ISS) / Ambulation Index (AI)

Disability and handicap were assessed using various scales. Handicap was measured using Rankin Scale. Disability was measured using DRS score, EDSS, ISS and AI. The EDSS measures the level of ambulation and the presence of somatic complaints on a scale of 0 to 10 (0 = no complaints or impairment; 10 = death). The AI gives an impression of walking ability on a scale of 0 to 9, with 0 being fully ambulatory and 9 being wholly restricted to a wheelchair and unable to achieve independent transfer. The ISS measures activities of daily living. This scale consists of 16 items concerning daily activities such as mobility, bowel and bladder function, and dressing. Each item is scored from 0 to 4 (0 = no impairment; 4 = patient is unable to perform task or needing maximal assistance). [53] UCAR et al. in a pre- and post-intervention study involving 30 patients with supraspinal spasticity and spasticity due to TBI reported significant reduction in the Rankin scale from a Mean ± SD of 5.91 ± 0.30 before treatment to 5.10 ± 0.56, $P<0.005$.[29, level II-2]

Francisco et al. reported that in five participants with a diagnosis of TBI, DRS scores changed from an average of 17.6 (SD, 5.1) before treatment to 15.6 (SD, 6.7) after ITB therapy. However, the change in DRS scores was not significant ($P = 0.75$).[32, level II-2] Zahavi et al. conducted a study involving 21 patients diagnosed with intractable spasticity of spinal origin to evaluate long term change in impairment, disability, and health related functional status. They reported a small but significant worsening in the level of disability (EDSS, AI and ISS). For EDSS, the Mean (SD): at baseline, 7.71 (0.81), at 26 weeks, 7.59 (0.86), at final assessment, 7.88 (0.91), $P = 0.023$ (final versus baseline). For AI, Mean (SD): at baseline, 7.74 (1.48), at 26 weeks, 7.64 (1.75), at final assessment, 8.05 (1.56), $P = 0.027$ (final versus baseline). For ISS, Mean (SD):at baseline, 25.74 (8.43), at 26 weeks, 25.27 (10.38), final assessment, 28.76 (10.36), $P = 0.011$ (final versus baseline).[53, level II-2]

Subjective Assessment of Function

Although other studies included in this review did not assess function with FIM / BIS / VAS / PEDI / GMFM, many subjective functional improvements were noted based on survey conducted using questionnaires or informal observation.

Krach et al. (2005), Mota et al. (2008), Krach LE, Nettleto A, Klempka B (2006), and Vender et al. (2005), conducted a survey using questionnaire to evaluate the subjects and their caretakers impressions as to the improvement in function after continuous ITB infusion.[21,49,59,58] Krach et al. in a follow-up of a RCT involving 31 CP patients reported improvement most often in motor control, positioning and endurance (60 to 70%). On the other hand, less than half observed improvement in speech, oral control, self-cares, transfers or walking.[21, level II-2] Mota et al. demonstrated that 17 out of 20 patients with CP (85%) reported a better use and improved ability in the upper limb, whereas no changes were found in three patients (15%). Reduced rigidity was reported in all 20 patients and 18 of them also experienced improvements during the rehabilitation sessions. Improvements were also reported in the management of daily activities. Level of independence was reported as improved in 90% of the patients.[49, level II-2]

Krach LE, Nettleton A, Klempka B (2006) conducted a survey involving 100 subjects (patients and caregivers). They found that 59% improved in ability to transfer, 74% in walking, 53% in use of arms, and 70% in ability to position. Improvement was also reported in ability to self-cares: 70% improved in dressing, 53% in toileting / hygiene, and 48% in feeding. Nearly half (47%) reported an improvement in general outlook of life. Startle movements and pain or discomfort were reported to improve in more than half (55% and 54% respectively). Improvement in ability to participate in activities was also noted:57% improved participation in recreational activities, 44% in video or computer activities, 41% spend time exercising outside therapy, 40% family or residential activities.[59, level II-3]

In contrast, Vender et al. in a cross sectional study involving 20 MS patients reported that on average, no significant differences in activities of daily living (dressing, eating, grooming, toileting, and bathing) were noted after pump treatment. Alterations in mobility did not occur after the surgery. Caregiver assessment involving 10 caregivers reported that seven out of 10 (70%) stated that the ability to take care for the patient after the pump placement was improved, two out of 10 (20%) stated that care was unchanged, and one out of ten (10%) stated that the ability had worsened.[58, level II-3] Subjective improvement in functions based on informal observation was reported in five studies.[23,24,26,32,41] Meythaler et al. (1999) reported that two out of six patients improved rapidly with respect to their functional status, improving from wheelchair-dependent to wheelchair independence with ambulation using assistive devices within two weeks of pump implantation. Another patient went from ambulation with assistive devices to independent ambulation without any devices and walks up to two miles per day.[23, level II-1]

Meythaler et al. (2001) reported improvement in 21 stroke patients. Three patients went from wheelchair dependence to independent ambulation with assistive devices. All dependent patients were more comfortable and were easier to manage at home with regard to hygiene, activities of daily living and assisted transfers.[24, level II-I]

Ordia et al. reported that several patients found that activities of daily living such as transferring from wheel chair to bed were easier to accomplish. Muscle aches and pain, sleeplessness, and overall misery associated with uncontrolled spasm were considerably improved. One college student's grades sharply improved because he was more alert after discontinuing large doses of oral antispasmodic medications. Several females found that maintaining personal hygiene was more satisfactory when they no longer had adductor spasticity and scissoring at the hips. Four reported that they were able to have sexual intercourse. Some male patients also found sexual intercourse easier. Four ambulatory patients were able to walk with less effort, whereas one patient who had previously been wheelchair bound became ambulatory. A number of patients who had previously felt embarrassed by their severe spasms in public were able to resume their social lives. Two previously unemployed patients became gainfully employed, one as a taxi driver. With fewer spasms eliminated, a number of patients took fewer sick days off from work.[24, level II-I2]

Francisco et al. reported that functional gains observed included decreased pain, improved activities of daily living, improved range of motion, improved motor skills, decreased primitive reflexes and faster gait speed.[32, level II-2] In another study involving 13 adolescents and adults with CP, Meythaler et al. (2001) reported that one patient after one year of treatment became independent with activities of daily livings and transfers and accepted full time employment. One patient achieved independence with feeding and was able to maneuver her power wheelchair independently for the first time. All dependent patients were more comfortable and were easier to manage at home with regard to hygiene, activities of daily living, and assisted transfers.[41, level II-2]

d. Quality of Life

Eight studies reported quality of life of patients treated with continuous ITB infusion for severe spasticity. Health related quality of life was measured using CHQ-PF50, SIP, HSCL, Ferrans and Powers Quality of Life Index, SSQL, and MSWS-12. The CHQ-PF50 is a generic child health instrument designed to measure the physical and psychosocial well-being of children aged five years and older. The CHQ comprises several domains that are scaled from 0 to 100. Higher scores reflect a better HRQL.[18] The SIP is a behavioural based self report measure that is used to quantify sickness related dysfunction. Patients are asked to complete a standardised questionnaire consisting of 136 items aggregated into 12 domains of daily functioning. A maximum possible score ranging from 0 to 100 (0 = no functional limitation for the category and 100 = maximal possible limitation).[25] HSCL consists of 57 items with two subscales and an overall scale. The subscale physical health contain eight items with scores ranging from 0 to 24 (0 = no complaints at all), the subscale mental health measures psychoneurotic complaints and consists of 17 items with scores ranging from 0 to 51 (0 = no complaints at all). [25] Ferrans and Powers Quality of Life Index is a 72 item toll that has four subscales: health & functioning, socioeconomic, psychological / spiritual and family. Higher scales indicate higher quality of life.52 The MSWS-12 was modified by substituting the effect of MS to the effect of pump implantation on 12 measures of ambulatory function.[55]

Table 12 and Table 13 summarises the findings of quality of life outcome. Table 12 showed that in children with CP, the CHQ-PF50 significantly improved for domains of bodily pain and discomfort, mental health and psychosocial status.[18, level I, 19, level II-2] Middel et al. reported significant improvement for sleep and rest, mobility, physical dimension, body care and movement, recreation and pastimes, and overall score of the SIP. The physical health and overall scale of the HSCL also showed significant improvement.[25, level II-2]

Similarly, Schiess et al. and Ivanhoe et al. reported significant improvement in quality of life of post stroke spastic hypertonia patients (Table 13).[46-47, level II-2] Significant improvement in SIP physical, psychological and overall score was also reported by Gianino et al.[52, level II-2] Improvement in quality of life was also seen in adult ambulatory patients with severe spasticity.[55, level II-2] In contrast Zahavi et al. reported no significant differences in HSCL and SIP with the exception for psychosocial dimension of SIP.[53, level II-2]

Table 12. Studies reporting quality of life outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Rating scale	Score Change from baseline to after treatment [Mean (SD)]
Hoving et al. 2009[18]	N = 17 (9 in CITB Group, 8 in Control Group) Children with CP. Mean age (SD):13.2 (2.8 years)	6 months	CHQ-PF50	• Score for bodily pain and discomfort improved with 24.4 (SD 20.7) in the CITB group and worsened with – 10.6 points (SD 26.8) in the Control group, P = 0 .014 • Score for domains of mental health improved 9.1 points (SD 9.1) versus Control group – 3.5 points (SD 15.1), P = 0.045 • Parental impact time improved by 5.2 points (SD 18.1) versus Control group – 19.8 points (SD 29.0), P = 0.043 • Psychosocial summary score (CITB group) improved 3.4 points (SD 7.9) versus Control group – 5.7 points (SD 8.8), P = 0.027
Hoving et al. 2009[19]	N = 17 children with CP.	12 months	CHQ-PF50	• Score for bodily pain and discomfort improved with 25.6 points (SD 35.9), P = 0 .016 • Score for domains of mental health improved with 9.8 points (SD 11.3), P = 0.007 • Score for domains of psychosocial status improved with 5.5 points (SD 9.0), P = 0.088
Middel et al. 1997[25]	N = 22 59% had MS, 41% SCI. Mean age (SD): 48.3 (12.7) years	12 months	SIP and HSCL	• Overall SIP score: ◦ 1 year, 25.13 (9.61) versus baseline, 31.28 (7.93), P = 0.005, effect size = 0.99 • SIP sleep and rest score ◦ 1 year, 13.99 (10.53) versus baseline, 20.48 (12.48), P = 0.01, effect size = 0.95 • SIP mobility score ◦ 1 year, 25.16 (19.50) versus baseline, 35.10 (19.64), P = 0.02, effect size = 0.73 • SIP physical dimension score: ◦ 1 year, 33.44 (12.73) versus baseline, 41.48 (8.07), P = 0.03, effect size = 0.86 • SIP recreation and pastimes score: ◦ 1 year, 30.53 (22.35) versus baseline, 42.47 (22.47), P = 0.04, effect size = 0.63 • SIP body care and movement score: ◦ 1 year, 41.44 (18.72) versus baseline, 50.62 (19.30), P = 0.02, effect size = 0.64 • SIP psychosocial score: ◦ 1 year, 10.96 (10.18) versus baseline, 14.80 (11.72), P = Not significant • HSCL total score: ◦ 1 year, 22.11 (12.09) versus baseline, 29.00 (12.71), P = 0.01, effect size = 0.87 • HSCL physical health score: ◦ 1 year, 3.66 (3.03) versus baseline, 4.89 (2.87), P = 0.01, effect size = 0.86 • HSCL mental health score: ◦ 1 year, 5.44 (4.57) versus baseline, 7.17 (5.56), P = Not significant

Abbreviation: CITB, continuous intrathecal baclofen infusion; SD, standard deviation; CP, cerebral palsy; MS, multiple sclerosis; SCI, spinal cord injury; CHQ-PF50, Child Health Questionnaire-Parent Form 50; SIP, sickness impact profile; HSCL, Hopkins symptom checklist.

Table 13. Studies reporting quality of life outcome after treatment with continuous intrathecal baclofen infusion for patients with severe spasticity

Study	Patients	Length of follow-up after treatment	Rating scale	Score Change from baseline to after treatment [Mean (SD)]
Schiess et al. 2011[46]	N = 30 Post stroke spastic upper and lower extremity. Mean age (SD): 52 (12) years	12 months	SSQL	• SSQL showed significant improvement specifically for the domains of family roles, mobility, personality, self-care, social roles, and work/productivity, P < 0.05 • No significant change in the domains of language, energy, mood, and vision
Ivanhoe et al. 2006[47]	N = 74 Post stroke spastic hypertonia. Mean age (SD): 57 (13.0) years	12 months	SIP	• Overall, mean total SIP scores improved significantly, P < 0.001 • Total SIP scores improved - 3.24 ± 9.10 (P = 0.003) from baseline to 3 months and - 4.32 ± 8.73 (P < 0.01) from baseline to 12 months • SIP scores improved significantly in both physical and psychosocial domains (P < 0.001). As compared with baseline, at 3 months, the physical and psychosocial domains improved - 2.24 ± 9.89 (P = 0.55) and - 4.51 ± 12.30, (P = 0.002), whereas at 12 months improvements were seen of - 4.55 ± 10.65 (P < 0.001) and - 4.91 ± 11.62, (P < 0.001), respectively.
Gianino et al. 1998[52]	N = 25 Spasticity of spinal origin. Mean age (SD): 39.4 (11.2) years	12 months	Ferrans and Powers quality of Life Index SIP	• Ferrans and Powers quality of Life Index: ◦ None of the changes in Ferrans and Powers QLI total or subscale scores for the different time points were statistically significant • SIP: ◦ Statistically significant difference between the baseline and 12 month SIP total score; 29.7 at baseline reduced to 21.2 at 12 months, P = 0.0042 ◦ 13 patients demonstrated improved physical subscale scores at 12 months, compared to baseline and 3 showed decline (P = 0.0213) ◦ 12 patients had improved psychological subscores at 12 months, compared to baseline, and 3 showed decline (P = 0.0352)
Zahavi et al. 2004[53]	N = 21 Spasticity of spinal origin. Mean age (SD): 54.6 (12.5) years	Mean: 84.9 months, (range, 66 to 108 months)	SIP HSCL	• No significant differences in HSCL and SIP with the exception for psychosocial dimension of SIP. • SIP (Psychosocial dimension): ◦ Baseline, 13.50 (10.39), 26 weeks, 10.88 (10.90), final assessment, 19.00 (16.91), final versus baseline, P = 0.18, final versus 26 weeks, P = 0.01
Sadiq et al. 2006[55]	N = 36 Adult ambulatory patients with spasticity.	1 to 13 years	MSWS-12	Compared 6 months post treatment and baseline: • 34 of 36 patients (94%) retrospectively stated that they would have no reservations about receiving the implant again and were overall improved • Based on the 12 items on QOL scale, only 2 patients (6%) had lower ambulatory score on one or more of the 12 items • 21 of 36 patients (58%) had improved scores on every item considered • ITB was beneficial in relieving pain in all 16 patients who had pain associated with spasticity • Symptoms such as spastic bladder and fatigue associated with lack of sleep were also generally improved

Abbreviation: SD, standard deviation; SIP, sickness impact profile; HSCL, Hopkins symptom checklist; SSQL, stroke-specific quality of life scale; MSWS-12, 12-Item MS

e. Quality of sleep

Four studies reported on quality of sleep. Bensmail et al. conducted a pre- and post-intervention study in 20 patients with severe spasticity to evaluate the effect of pump-infused ITB in therapeutic doses on sleep quality and on day time and night time respiratory function. They found that ITB improved total sleep time (P = 0.05),improved sleep continuity, thereby improving sleep efficiency (P = 0.01), and reduced periodic leg movements (P = 0.02). ITB increased the percentage of REM sleep but did not modify delta sleep. ITB did not modify sleep-related respiratory events, CO_2 rebreathing response, or the resting energy expenditure.[57, level II-2] Gluglielmino et al. also reported significant improvement in quality of sleep. The mean before ITB treatment was 2 and after ITB treatment was 4, P < 0.01 (based on 5 point VAS scale; 1 worst condition to 5 best condition).[31,level II-2] Ramstad et al. reported significant reductions in number of awakenings during the first six months of continuous ITB infusion treatment, from a Median (range) of 1.0 (0-25) to 0.0 (0-10), P = 0.005.[30,level II-2] Vender et al. reported improvement in ability to sleep to a score of 5.8 after surgery (1, extremely difficult; 3, somewhat difficult; 5, expected; 7, better than expected; and 9, no difficulty).[58, level II-3]

f. Treatment goals

In the assessment of a treatment, distinction needs to be made between goals, which are what the patient and caregivers wish to be achieved, and the actual outcomes. Gray et al. conducted a pre- and post-intervention study to evaluate the success of goals and compared these to actual outcomes in 37 non ambulant children with severe spasticity receiving continuous ITB. Prior to pump insertion, three specific goals were set between the caregiver, physiotherapist and if possible the child, which were considered to be important and realistic. Goals included function, ease of care, mood, or the prevention of deformity. They reported that all three set goals were attained by 80% of children at nine and 18 months. The most common successful outcomes were ease of nursing care, better sitting, spasm reduction, more relaxed / better mood, and improved sleep.[27, level II-2] Campbell et al. reported that of 108 initial treatment goals, 101 (94%) were at least partly achieved and 78 (72%) were completely or almost completely achieved. Treatment goals included improvement in function (independent mobility and self-help skills), comfort (pain reduction and being able to sleep better and sit longer), and care-giving (dressing and positioning). All families interviewed identified some goals that were achieved.[40, level II-2] In another study involving 100 subjects / caregivers Krach LE, Nettleton A, Klempka B stated that regarding all goals; 71% reported they were fully met, 14% partially met, and 15% either unsure or not met.[59, level II-3]

g. Satisfaction of treatment with continuous ITB infusion

Satisfaction of treatment with continuous ITB infusion was reported in four studies. In order to assess the overall satisfaction, Hoving et al. stated that during the last follow-up, children and their caregivers were asked whether they would participate in the test treatment and implantation procedures again. They found that 15 of the 17 children and / or their parents (88.2%) stated that they would participate in all procedures again. Two parents were not sure, in spite of the achieved individual treatment goals for their children.[19, level II-2] Motta et al. investigated the degree of satisfaction with the treatment through two questions: the first refer to the actual satisfaction with the therapy, by selecting only the following three options; very satisfied, satisfied, or dissatisfied, and the second question is aimed to find out whether the patient would resubmit to implantation of the intrathecal infusion system. They reported that 18 out of 20 patients (90%) expressed satisfaction with the procedure, and most patients (18 of 20) would do it again.[32, level II-2] Zahavi et al. reported that 19 out of 21 patients (90.5%), were satisfied with the overall treatment and indicated that they would recommend the treatment to other patient with spasticity. Of the two patients who were not satisfied with the treatment, one had experienced five recent episodes of catheter dysfunction, and one acquired an allergy.[53, level II-2] Similarly, Krach LE, Nettleton A, Klempka B reported that 82% indicated they would implant a pump again, 12% indicated that they would not and 6% were uncertain.[59, level II-3]

h. Hospitalisation

Ordia et al. conducted a pre and post-intervention study involving 59 patients with severe spasticity of spinal origin to determine the efficacy, safety, and cost-effectiveness of ITB. For the cost study, the first 10 eligible patients to give consent were studied. They reported that there was a reduction in the average length of hospitalisations, but no change in the overall utilisation of outpatient resources during the first year after the pump was implanted. For the year prior to the implantation, excluding days spent on screening, the 10 patients had 12 hospitalisations with an average length of stay of 7.9 days, for a total of 95 days. For the first year post implantation, excluding the implant itself, they had 12 hospitalisations, with an average length of stay of 5.7 days, for a total of 68 days. The net reduction in hospital days was 27, for an average reduction of 2.7 hospital days per patient.[26, level II-2]

i. Hip subluxation / hip dislocation

Krach et al. conducted a prospective, non controlled, open-label, multi centres study to assess whether reduction of muscle tone by continuous ITB infusion affects the progression of hip subluxation in persons with CP. Thirty three subjects had hip x-rays before and one year after pump implantation. The primary outcome measure was change in absolute hip migration percentage and the secondary outcome measure was change of migration percentage class. They found that 33.3% of hips had an increase of absolute migration percentage of 5% or more; 12.1% of hips had a decrease of migration percentage of 5% or more; and 54.5% of hips remained unchanged. Overall, 90.9% of hip manifested no deterioration or had improvement of their migration percentage class during the year of intrathecal baclofen therapy. Reduction in muscle tone with continuous ITB may slow or prevent the development of hip subluxation and dislocation in persons with CP.[60, level II-2] Silva et al. conducted a study to compare the rate of hip dislocation and the need for further hip surgeries in SDR and continuous ITB infusion for non ambulatory CP patients. They reported no significant difference in the rate of secondary hip reconstructive surgery or dislocation between non ambulatory cerebral palsy patients who underwent SDR versus continuous ITB infusion. Hip dislocation rate was 10.6% (10/94) in the SDR group and was 7.4% (7/94) in the continuous ITB infusion group. Reconstruction was required in 25% to 32% of hips despite spasticity intervention with either procedure.[61, level II-2]

j. Mortality

Krach et al. conducted a matched cohort study to determine whether ITB changes mortality risk in persons with CP. Records were reviewed for all persons with CP who were managed with ITB for hypertonicity at a specialty hospital in Minnesota between May 1993 and August 2007. A comparison cohort with CP was randomly selected from clients of the California Department of Developmental Services who were initially evaluated between 1987 and 1990 and were matched to those with ITB for age, sex, Gross Motor Function Classification System (GMFCS) level, presence or absence of epilepsy, and feeding tube-use. Survival probabilities were estimated using the Kaplan-Meier method, and differences were tested via log-rank. Three hundred and fifty nine persons with CP receiving ITB were matched to 349 persons without ITB. Survival at eight years of follow-up was 92% (SD,1.9%) in the Minnesota ITB cohort and 82% (SD,2.4%) in the California non ITB cohort, P<0.001. After adjustment to account for recent trends in improved survival in CP, 8-year survival in the non-ITB cohort was 88%, which was not significantly different from the ITB cohort (P = 0.073). The authors concluded ITB therapy does not increase mortality in individuals with CP and may suggest an increase in life expectancy. [62, level II-2]

6.1.2. Safety of continuous ITB infusion for treatment of patients with severe spasticity

Forty articles (studies) reported complications or adverse events related to continuous ITB infusion for treatment of patients with severe spasticity.[19,20,22,24,26-29,31,33-40,42-44,48-49,51,54-55,58,63-76] Complication rates vary in published studies. Complications were either drug or device related. Device related complications were classified as either related to the surgical procedure or to the system (catheter or pump).[20] Complications reported ranged from mild to severe. There were no deaths related to continuous ITB infusion reported in any of the studies.

a. Drug related adverse events

The most frequent drug related adverse events reported include hypotonia, somnolence, headache, nausea, vomiting, dizziness, seizures, constipation, bradycardia, and urinary retention. These were often transient and reversible.[19-20,22,24,27,34,35,40,43-44,48,63]

Drug tolerance

Ordia et al. reported drug tolerance occurred in one out of 59 patients (1.7%) with MS 21 months after the pump was implanted. Dose of ITB administered increased from 520 µg to 800 µg daily over a two-month period. Radiographic and radionuclide studies showed the system to be patent. He was given a one-month drug holiday from intrathecal baclofen, during which he received 2 mg of intrathecal morphine daily. When intrathecal baclofen was resumed, he had an excellent response to 100 µg daily.[26, level II-2] Natale et al. reported that four out of 112 patients (3.6%) developed tolerance and they were weaned and kept off ITB for four to six weeks drug holiday. During this time intrathecal morphine was administered. When ITB was restarted, the effective dose was less than half the dose to which they had been tolerant and this low dose has been continued for three to four months before requiring an increase.[28, level II-2] Gluglielmino et al. reported that in one out of 30 patients (3.3%), rapid baclofen tolerance was observed two days after ITB implantation. Infusion of baclofen was stopped ("baclofen holiday") and switched to morphine for 10 days to achieve receptorial baclofen washout before resuming ITB therapy. On day 11, ITB therapy was resumed and yielded good response.[31, level II-2] Ochs et al. reported that tolerance occurred in only one out of 28 patients (3.6%), whereby there was a 500% increase of the dose necessary.[43, level II-2] Heetla et al. conducted a retrospective long term follow-up study to quantify the incidence and management of tolerance in patients treated with ITB therapy. All patients treated with ITB at the departments of neurology and neurosurgery of the University Medical Centre, Groningen from 1991 to 2005 was screened for the study. If patients showed tolerance they were offered three treatment options: switch to complex continuous infusion, switch to pulsatile bolus infusion, or drug holiday. They found that 8 out of 37 patients (22%) developed tolerance, defined as dose increase of >100 µg per year. No predictive factors for the development tolerance could be determined. Strategies to treat tolerance showed that altering the infusion mode from simple to complex continuous (n = 6) had no effect on the development of tolerance, while pulsatile bolus infusion (n = 1) and drug holiday (n = 20) were both effective in reducing the daily baclofen dose.[71, level II-3]

Baclofen overdose

Azouvi et al. reported severe side-effects which were probably related to baclofen overdose in two out of 18 patients (11.1%). They were characterised by somnolence and muscle flaccidity. Both patients were hospitalised, one received mechanical ventilation. This patient received baclofen by a mechanical pump and probably made a mistake in pump management, which provoked an overdose. From then on, treatment was definitively withdrawn. The other patient developed problems after a single bolus of 130 µg, without any other explanation. Treatment was continued with a lower dosage without any side effect.[44,level II-2] In another study, Gooch et al. reported that one out of 100 patients with spastic diplegia CP (1.0%) had an ITB overdose following an incorrect bolus injection after catheter replacement. Shortly after the bolus, the patient developed respiratory depression. The patient was intubated and ventilated for approximately eight hours and recovered without sequelae.[63, level II-2]

Delirium secondary to intrathecal baclofen

Castano et al. conducted a case control retrospective study to describe the psychiatric manifestations due to intoxication or withdrawal of ITB and to explore the possible risk factors for the presentation of delirium secondary to baclofen. They found the frequency of delirium secondary to ITB was 9.5% (12/126 patients) in the 14 years of follow-up. Eight cases (66.6%) were due to intoxication and four cases (33.3%) were due to withdrawal. A total of three out of 12 patients with delirium (25%) had a fever at the time of the onset of the psychiatric symptoms. There were no fatal cases due to delirium. Intoxication symptoms coincided with the first filling of the pumps in four patients, after pump refill in two patients, and after a dose increased during a refill in two patients. Withdrawal causes were due to empty pump reservoir in two cases and end of battery life in two cases. The average time from pump implantation to the presentation of the intoxication symptoms was eight months (from day 1 to 4.5 years), while the average time from pump implantation to the presentation of withdrawal symptoms was 7.4 years (from 4.9 to 9.9 years), P = 0.016. Psychiatric manifestations were present for one to three days in 75% of the patients with delirium. In the intoxication group, symptoms did not persist beyond the third day and roughly 25% of these patients had symptoms for less than 24 hours.

This findings were opposite of those in patients with withdrawal. In this group, no patients had symptoms less than 24 hours and 25% of patients presented symptoms for more than three days. Intoxication was characterised by visual hallucinations with disorientation and insomnia. In the clinical pattern of withdrawal, confusion with hallucination and delusions was more prominent. These patients unlike the cases of intoxication, did not present with agitation, drowsiness or disorientation. The therapeutic interventions used consisted mainly of modifications of the ITB dose and supportive measures.[63, level II-2]

Seizures

Seizures were reported as adverse events in few studies. Hoving et al. reported two epileptic seizures whereby one was considered as serious.[19, level II-2] In the study by Gilmartin et al., seizures were reported during titration and maintenance phase and all patients who experienced seizures had a history of seizures. No seizures were reported during the screening phase of the study.[19, level II-2] Awaad et al. reported increased seizure frequency in two patients and new onset of seizures in two other patients (all of them had underlying brain pathology).[35, level II-2] In another study, Becker R, Alberti O, Bauer BL reported that one patient had an epileptic seizure with the first bolus application of baclofen. It was a single event and there were no further convulsions.[42, level II-2]

Buonaguro et al. conducted a pre- and post-intervention study with control group to analyse the relationship between epilepsy and ITB therapy in children with CP or spasticity of cerebral origin. In the study group; 60 out of 150 children (40%) had epilepsy before ITB, while 90 out of 150 children (60%) without epilepsy. In the control group there were 37% of children with epilepsy and 63% without it, (odds ratio between ITB and control group regarding epilepsy was 1.13, 95% CI: 0.67 to 1.91). In the ITB group, eight out of 60 children (13.3%) with prior epilepsy manifested an improvement after ITB in seizure frequency, whereas two children worsened and one child had seizures ex novo. Four of these eight children experienced seizure remission and discontinuation of antiepileptic treatment. No significant differences were evident among children who improved or worsened regarding sex, AS, clonus, and spasms. The authors concluded that in children with spasticity of cerebral origin, ITB does not seem to aggravate or induce seizure activity.[68, level II-2]

Schuele et al. conducted a pre- and post-intervention study with matched control to assess the prevalence of epilepsy in a cohort of patients with long-standing MS and the potential effect of ITB on seizure frequency. They also compared the incidence of newly occurring seizures in a group of patients with MS treated with ITB with that of matched controlled group. They found that seizure frequency was less than once per year, and there was no noticeable change in seizure frequency detected after initiation of ITB therapy. During the observation period, new onset of epileptic seizures was seen in seven patients in the ITB group and in one patient in the control group, $P < 0.05$. Among the seven patients with new seizures in the ITB group, five patients had a single event, all associated with additional aggravating factors: febrile illness, accidental baclofen overdose, serum sodium of 124 mmol/L, and post- operative setting. Two patients developed recurrent seizures, both with more than three seizures per year and in one it was associated with recurrent febrile urinary tract infections. Two patients developed single episode of non convulsive status epilepticus (NCSE), and one demonstrated recurrent focal motor status epilepticus after initiation of ITB therapy. The first patient developed NCSE immediately after baclofen pump implantation due to accidental overdose of 10-fold the programmed initial bolus. The second patient developed NCSE in the setting of sepsis three months after pump implantation. The third patient developed recurrent focal motor status epilepticus 2.5 years after ITB therapy was initiated. The epileptic events repeatedly occurred in the setting of febrile urinary tract infections and resolved with antibiotics and antiepileptic therapy while ITB treatment was continued.[69, level II-2]

Sexual function

Jones et al. conducted a pre- and post-intervention study at Atlanta Georgia to examine prospectively with a standardised measure of sexual function, the impact of intrathecal baclofen on perceived sexual functioning in men with severe spasticity of spinal origin. Seven adult men with SCI who received ITB through an implantable pump for treatment of severe spasticity were followed for an average of 670 days (22.4 months) after implant. Perceived sexual function was assessed using Brief Sexual Function Inventory (BSFI).Participants indicated generally unchanged or improved ratings of perceived sexual functioning after implant. Two out of seven participants reported some negative changes in sexual function after baclofen pump implant, noted in the areas of reduced sex drive and problems with erections (frequency, rigidity, difficulty in achieving). Two participants reported marked improvement in perceived sexual function from pre to post implant. Analysis of changes in perceived sexual function over time suggest that problems may be associated with an increase in baclofen dose and may be reversible with a reduction in dose. The authors concluded that ITB may impact perceived sexual function particularly at higher doses. However, the effects seemed to be reversible with withdrawal or reduction of baclofen administration.[75, level II-2]

Another study was conducted by Denys et al. involving nine consecutively recruited men with SCI or MS who were receiving ITB by an implantable pump. Genitosexual function was assessed clinically with a questionnaire given to the patient during personnel interview before pump implantation and after pump implantation. The questionnaire focused on the following aspects: the ability to sustain reflexive and psychogenic (without any local stimulation) erections and to obtain ejaculation without any electrical, vibratory or pharmacologic stimulation, assessed by a yes / no score; penile rigidity during erection, evaluation by a visual analogue scale on which 100% meant maximal rigidity and 0% no erection at all. Patients were also questioned about possible modification of libido before and after implantation. Patients reported that Libido and the ability to obtain erection by psychogenic or reflexogenic means were not modified during treatment with ITB. However, eight patients reported a decreased of erection rigidity and / or duration. Ejaculation was possible in three cases before implantation, it disappeared in two patients, and more difficult to obtain in the last one. In the two patients ejaculation reappeared during temporary unexpected treatment withdrawal (because of catheter or pump dysfunction). There were no differences between MS and SCI patients. The authors concluded that ITB may seriously compromise erection and ejaculation. In most cases, the beneficial effect on spasticity outweighed the deleterious effect on sexual function. None of the patients asked for treatment interruption. It should be stressed that the inhibitory effect is reversible. Nevertheless, patients should be informed on this possible effect (as well of its reversibility), which should be considered before any decision on pump implantation.[76, level II-2]

b. Device related adverse events

Surgical procedure related adverse events frequently reported were pocket seroma, pocket infection, CSF leak, surgical wound infection, and programming errors.[19-20,26,27-29,33-38,40,42-43,48,51,54,66] Several technical issues related to catheter and pump were reported (catheter break, catheter kink, catheter dislodged, catheter occlusion, catheter ruptured, catheter migration, back pain at catheter site and pump malfunction). Complications can usually be easily corrected surgically. However, some required explantation or replacement of the device.[20,22,24,26,27-29,31,35,39,40,42-43,49,54-55,58,63,66]

Infections

Borowski et al. conducted a pre- and post-intervention study in 174 children with CP treated with ITB to investigate and evaluate complications of ITB pump implantation and maintenance. Acute infection within 60 days of surgery and late infection rates were calculated on the basis of the number of incidents and incidents/ follow-up patient years, respectively. There were 78 procedures in 57 patients related to complications, and the acute infection rate was 4.0%. The probability of developing a late infection was 1.0% per year of follow-up.[64, level II-2] Wunderlich CA and Krach LE conducted a cross sectional study to describe signs, symptoms, and clinical outcomes of individuals undergoing ITB therapy who experienced pump-related Gram-negative infections including meningitis. A total of 571 baclofen pump surgeries were performed from 1996 to 2003, with 45 infections. Of the 45 total infections noted in the chart review, 12 were Gram-negative infections. Only two of these 12 Gram-negative infections resulted in meningitis; the other 10 were combinations of pocket, back wound and skin infections. Ten out of 12 Gram-negative infections (21 site encounters) occurred within 60 days of surgery. Eleven of the 12 pumps were explanted. By site encounters, *Pseudomonas aeruginosa* accounted for eight Gram-negative infections, *Escherichia coli* for five, *Proteus* for three, *Enterobacter cloacae* for two, and *Klebsiella*, *Enterobactor aerogenes*, and *Enterobactor vulnaris* for one each. Two individuals with Gram-negative meningitis were admitted 72 to 96 hours after hospital discharge following pump replacement. Both patients had a rapid deterioration requiring transfer to the paediatric intensive care unit, and developed coagulopathy and decrease in responsiveness. Both have improved and have elected not to replace the ITB pump.[65, level II-3]

Fjelstad AB, Hommelstad J, Sorteberg A conducted a cross sectional study to determine the frequency of infection and to identify risk factors for infection in connection with the implantation of an ITB pump. This retrospective study included all paediatric and adult patients (163 patients) who received ITB at Rikshospitalet during the years 1999-2005. A total of 408 surgical procedures were performed. When a pump was implanted subsequent to a screening trial with transcutaneous catheter insertion, the rate of infection was 9% in the paediatric patients. The corresponding infection rate for pumps implanted after a screening trial with a subcutaneous distal catheter (Albright Method) was 12%. This difference was not significant. They reported significantly higher incidence of deep infections following pump implantation in the paediatric group (10%) than in the adult group (0%), P = 0.02. The presence of percutaneous endoscopic gastrostomy (PEG) tube increased the incidence of infection, P = 0.008 and may be one of the main reasons for a higher frequency of infection in children. When the patient suffered urinary and / or faecal incontinence, there was a higher chance of infection, P = 0.021.The most common causative agent was *Staphylococcus aureus*; responsible for 69% of deep infections. Sixty nine percent of deep infections occurred within one month after surgery. The authors concluded that the rate of infection is significantly higher in children undergoing ITB pump implantation than it is in adult. Screening trials applying the Albright method fail to reduce the frequency of infection subsequent to pump implantation. The presence of PEG tube has the greatest significance as a predictor of infection.[67, level II-3] Infections were also reported by other studies.[29,35,54,66]

Progression of scoliosis

Three studies reported the impact of ITB on the natural history of scoliosis in CP patients.[72-74] Ginsburg GM and Lauder AJ conducted a pre- and post-intervention study to quantify scoliosis progression in spastic quadriplegic patients before and after ITB administration and compared this to published natural history data. Each patient had at least two pre and post pump insertion spinal radiographs made to document the rate of scoliosis progression. They reported that the average Cobb angles was 10.2°(SD, 6.4°) before pump insertion and 25.0°(SD, 18.9°) at an average of 20.9 months after pump insertion, P< 0.0001. The mean rate of change in Cobb angles was 1.825%/ year (SD, ± 2.2°/year) before pump insertion and 10.95%/year (SD, ± 14.6°/year) at an average of 23.9 months after pump insertion (P = 0.024). These results represent a 6-fold increase in the curve progression rate after pump insertion. There was no association between catheter tip location or rate of baclofen infusion on curve progression. The authors concluded that in published data, the rate of progression of scoliosis in skeletally immature non ambulatory patients with cerebral palsy was 4.5°/year. In this study average rate of progression of the scoliosis for the immature was 9.02°/year. For the skeletally mature bed-ridden patients, the worst-case natural history progression was 4.4°/year. The comparable rate of change in skeletally mature (Risser 5) non ambulatory patients in this study was 28.4°/year. This study demonstrated a significant increased in the rate of scoliotic curve progression after ITB pump placement when compared with published natural history data.[72, level II-2]

Senaran et al. conducted a pre-and post-intervention study with matched control group. All patients with spastic CP treated with ITB between 1997 and 2003 at a single institution were reviewed. A total of 107 patients undergoing ITB for a minimum of two years were identified, of which 26 patients subsequently developed or had a progression of scoliosis. Twenty five; age, gender, and GMFCS score-matched quadriplegic CP patients with scoliosis who did not receive ITB were selected from a database and constituted the control group used to compare the rate of curve progression and pelvic obliquity. They found that the average curve progression for the baclofen group after pump implantation was 16.3º per year, and for the control group was 16.1º per year. Both groups curves progressed over time during growth (P = 0.001), but baclofen did not have an independent effect on curve progression (P = 0.181). The average pelvic obliquity for the two groups increased over time (P = 0.001), but there was no significant difference between the two groups, P = 0.536. In the Baclofen group, 57 patients had no scoliosis or curve < 15° at pump implantation. Twelve of the 57 patients (21%) developed scoliosis after pump implantation during a mean of 3.6 years of follow-up. Thirty out of 92 matched control patients (32%) not treated with ITB within the same interval had scoliosis by maturity.

The authors concluded that this study demonstrates that ITB has no significant effect on curve progression, pelvic obliquity, or the incidence of scoliosis when compared with an age, GMFCS score matched control group.[73, level II-2] Similarly, Shilt et al. reported that there was no statistically significant difference between the mean change in Cobb angle in ITB patients (6.6° per year) compared with the matched control patients (5.0°per year), P = 0.39. Multiple linear progression showed that adjusting for age, sex, topographic involvement, and initial Cobb angle, the mean progression of Cobb angle was 0.92°per year greater in ITB group compared with controls, P = 0.56. The authors concluded that the progression of scoliosis in CP patients with ITB treatment is not significantly different from those without ITB treatment. The findings suggest that patients receiving ITB experience a natural progression of scoliosis similar to the natural history reported in the literature.[74, level II-2]

6.1.3. Cost-effectiveness analysis / cost-utility analysis of continuous ITB infusion for treatment of patients with severe spasticity

There were limited retrievable studies related to the cost-effectiveness analysis (CEA) / cost-utility analysis (CUA) of continuous ITB infusion for treatment of patients with severe spasticity. In this review, we included four CEA / CUA conducted in Netherlands, U.S.A, France, and Japan.[77-80]

A combined CEA and CUA were conducted in Netherlands to evaluate the cost-effectiveness of CITB in the treatment of children with intractable spastic CP. This combined CEA and CUA were embedded in the Dutch national study on the efficacy and safety of continuous ITB (CITB) for intractable spasticity in children with CP. The study compared the costs and health effects of CITB and standard treatment only, for a one year period. Patients received only standard treatment in the year preceding the test treatment versus CITB in addition standard treatment from the pump implantation onwards. Standard treatment included physical therapy, and / or rehabilitation. For the assessment of the additional costs of CITB, the costs in the year before the test treatment were compared with the costs in the first year after the pump implantation (before-after comparison). For the assessment of the additional health effects of CITB, the VAS was used for individual problems in the CEA and the EuroQoL-5D (EQ-5D) in the CUA. They compared the values at the one-year follow-up visit with those obtained before pump implantation (baseline). The perspective of both the CEA and CUA was that of the health care. Costs were estimated for the year 2003 in Euros. Costs that were not available for the year 2003 were discounted at 4% per year according to Dutch guidelines. Bootstrap method was used to verify the reliability of the results. They mean health care costs were £5,296 for the year during which the study participants received standard treatment only and £9,028 for the year during which the participants also received CITB. The mean additional annual health care costs of CITB were £3,732. The VAS for individual problems improved from 2.3 (SD, 1.1) at baseline to 7.2 (SD, 1.7) after one year of CITB (P = 0.001). On the cost-effectiveness plane, all point estimates were found in the same quadrant. This means that CITB was more effective and more costly than standard treatment only. On the cost-utility plane derived from the Dutch EQ-5D index, all point estimates were found in the same quadrant. This means that CITB was more effective and more costly than standard treatment only. The cost utility plane derived from the UK EQ-5D index showed no appreciable difference. One QALY cost an average £32,737, using the Dutch EQ-5D index, and £28,273, using UK-5D index. The authors concluded that our results confirm the cost-effectiveness of CITB for carefully selected children with intractable spastic CP and, from an economic point of view, justify the reimbursement of CITB for this group of patients in the Netherlands (threshold willingness to pay for one QALY in the Netherlands, £80,000).[77]

de Lissovoy et al. conducted a CUA in the U.S.A to assess the cost-effectiveness of intrathecal baclofen among children with severe spasticity of cerebral origin who have not responded to less invasive treatments such as oral medications relative to alternative medical and surgical therapy. Mathematical modelling and computer simulation were used to estimate the incremental cost per quality-adjusted life-year for identical cohorts of 20 children treated with ITB or alternative therapy over 5-year episode of treatment. Data on treatment costs representative of these children were derived from a health insurance claims database that included both commercial and Medicaid data. Utility values used to construct quality-adjusted life years were obtained from a panel of nine expert clinicians who used the Health Utilities Index-2 to rate health states associated with course of treatment. In the base case, ITB therapy cost an average USD $ 49,400 more than the alternative medical therapy over a 5-year period. However, this was accompanied by an average gain of 1.2 quality-adjusted life-years. The net result was incremental cost-effectiveness ratio of USD $ 42,000 per quality-adjusted life-year, (interquartile range, USD $ 36,700 to USD $ 62,200) per QALY, a figure well within the USD $ 50,000 to USD $ 100,000 range that is widely accepted as offering good value for money. The authors concluded that our results indicate that ITB delivered via an implantable pump in appropriately selected paediatric patients offers a good value for the money based on widely accepted measures of cost-effectiveness.[78]

A study was conducted in France by Bensmail et al. to assess by simulation the cost-effectiveness of ITB as a first-line strategy compared with conventional medical treatment for patients with disabling spasticity and functional dependence caused by any neurological disease. Two simulation models were created to simulate therapeutic strategies for managing severe spasticity: one with the use of ITB and one without the use of ITB, to assess various treatment sequences over two years based on current medical practices in France. Successful treatment at each evaluation was defined as a combination of: (1) the increased patient and caregiver satisfaction as assessed by goal attainment scaling (GAS), and (2) a decreased of at least one point on the AS score. Probabilities sensitivity analysis were performed using 5000 Monte-Carlo simulations taking into account specific distribution curves for direct costs and effectiveness parameters in each treatment option. The model simulation established that using ITB as a first option strategy in the management of function of severely impaired patients with disabling spasticity results in significantly higher success (78.7% versus 59.3%, P < 0.001). In addition, the ITB therapy model revealed a lower cost (£59,391 versus £88,272; P < 0.001) and an overall more favourable cost-effectiveness ratio (£75,204/success versus £148,822/success, P < 0.001) compared with conventional medical management without ITB. The authors concluded that within the assumptions of our modelling, ITB therapy evaluated by a combination of treatment success criteria at six-month interval over a two-year period maybe a cost-effective strategy compared with conventional medical management alone.[79]

Hattori N, Hirayama T, Katayama Y conducted a CUA of ITB by time period in six severely spastic patients admitted to Nihon University School of Medicine, Tokyo between 2005 and 2010 for ITB therapy. Six subjects underwent a primary survey one year after surgery. The degree of spasticity was evaluated before and one year after surgery using AS score. Activities of daily living were evaluated using modified Rankin scale. Quality of life was evaluated before and one year after surgery according to EQ-5D Japanese version using information obtained from the patients themselves. The medical costs were divided into direct cost (DC) and indirect cost (IC). The DC was based on the charges made by the hospitals and clinics for each patient and adjusted to the cost in April 2009. The IC was calculated on the basis of the estimated production loss of the patient and their family members who were responsible for nursing at home, using the Wages Census, a fundamental statistic of wages and salary structure (2009). Utility scores before and after surgery was multiplied by the number of years of activity to calculate the quality-adjusted life years (QALY) for each patient. Sensitivity analyses were performed to consider the effect of changes in costs (discount rate, 0 - 10%). They reported significant improvement one year after surgery in terms of: Mean Modified Rankin scale, 3.83 before ITB decreased to 2.33 after ITB therapy; Mean AS score, 3.17 before ITB decreased to 2.04 after ITB therapy; quality of life value (utility) was 0.242 increased to 0.662 after ITB therapy. Direct medical costs/month was 37,500 Japanese yen before ITB, increased to 46,000 Japanese yen after ITB therapy. Indirect medical costs/month was 613,170 Japanese yen before ITB decreased to 511,443 Japanese yen after ITB therapy. The average cost of ITB therapy per QALY five years after surgery was 1,554,428 Japanese yen, well below the six million yen willingness-to-pay threshold for one QALY. The authors concluded that this study shows that ITB therapy in Japan is an outstanding treatment in medicoeconomic terms.[80]

6.1.4. Daily Dosing

The daily dose of intrathecal baclofen required to maintain the therapeutic effect increased in all of the studies, from the start of the study to its completion. The average daily dose of baclofen to achieve reduction range from 205.3 µg/day to 591.5 µg/day at the most recent follow-up.[20,23-24,27,32-33,37-38,41,43-44,51]

6.2. DYSTONIA

Six articles (studies) related to the effectiveness and safety of continuous ITB infusion for treatment of patients with severe dystonia met the inclusion criteria and included in this review.[81-86] The included studies comprised of five pre- and post-intervention studies and one observational study. There was no CEA / CUA of continuous ITB infusion for treatment of patients with severe dystonia retrieved. The articles were published between 1996 and 2009. Two studies were conducted in Italy, three in the U.S.A, and one in the United Kingdom. Continuous ITB infusion was used to treat primary and secondary dystonia. The total pooled sample size of all included studies was 163 subjects. Sample sizes of each of the included studies ranged from 8 to 86. The length of follow-up ranged from six months to 64 months.

Risk of bias

The pre- and post-intervention studies have clear and consistent inclusion and exclusion criteria in subject selection. Cross sectional study have potentially higher risk of bias

6.2.1. Effectiveness of continuous ITB infusion for treatment of patients with severe dystonia

There are two evaluation tools used to evaluate dystonia. The Barry-Albright Scale (BAD) and the Burke-Fahn-Marsden (BFM) rating scale. The BAD evaluated secondary dystonia in eight regions of the body (eyes, mouth, neck, trunk, upper limbs, and lower limbs) and gives each a score from 0 to 4. The score reflects the duration of the dystonia and the degree to which this interferes with the everyday activity of the patient. The BFM was created to evaluate primary dystonia but can also be used for secondary dystonia and consists of two sections; the movement scale, based on the patient observation, and the disability scale, based on the patient's everyday activity. The movement scale score is the sum of the individual scores obtained for each of the nine assessed areas of the body (eyes, mouth, neck, trunk, upper limbs, lower limbs, speech-swallowing). The individual score for each region of the body is a combination of two factors (the provoking factor and the severity factor), each of which is evaluated with a scale from 0 to 4. Score varies from a minimum of 0 to a maximum of 120. The second scale, the disability scale, considers seven areas of the patient's daily activities (speech, handwriting, feeding, eating and swallowing, hygiene, dressing, walking), with maximum score of 30. A low score equates with less dystonias in both scales.[81] Functional outcome was also assessed by subjective questionnaire.

a. Dystonia outcome

Barry-Albright Scale (BAD)

Motta et al. (2008) conducted a pre- and post-intervention study involving 19 patients affected by dystonia as an outcome of infant CP belonging to level V GMFCS treated with ITB. The difference between the follow-up and preimplant scores showed a statistically significant improvement, which was apparent after three months and which was maintained for the 12 months of follow-up. The average BAD score of 23.84 (SD, ± 4.11) at baseline was decreased to an average of 17.79 (SD, ± 3.3) at 12 months postimplant. At 12 months postimplant, the average BAD total score showed an improvement of 25% compared with baseline in all patients.[81, level II-2] In another study by Motta et al.(2009) involving 11 patients with secondary dystonia, classified as levels 3 and 4 GMFCS, they found that dystonia decreased significantly by 15% from baseline to 12 months follow-up ($P < 0.05$). At baseline, the average percentage of BAD total score was 63.35 (SD, ± 19.9) reduced to 48.01 (SD, ± 14.9) at 12 months post implant. The BAD score related to upper limbs decreased from 6.7 (SD, ± 1.2) at baseline to 5 (SD, ± 1.3), $P < 0.05$. Specifically, it decreased in eight out of 11 patients (73%) and remained the same in others.[82, level II-2] Albright et al. reported significantly lower BAD scores at each time interval after ITB implantation than baseline in a pre and post-intervention study involving 86 participants with generalised dystonia. The mean and median BAD scores at baseline were 18. The mean score at three months was 13, $P = 0.003$; at six months was 10, $P = 0.001$; at 12 and 24 months was 7, and 10, respectively, $P \leq 0.001$. The mean dystonia scores were significantly lower in participants whose intrathecal catheters were positioned at T4 or higher compared to those at T6 or lower, (BAD Score; 4 versus 10, $P = 0.005$). Ninety two percent of participants retained response to ITB during a median follow-up of 24 months, 8% lost their response during chronic treatment usually during the first year after implantation.[83, level II-2]

Burke-Fahn-Marsden (BFM) rating scale

Motta et al. (2008) reported statistically significant overall improvement in BFM ($P < 0.001$). The total BFM score decreased from a baseline of 98.57 (SD, ± 13.07) to an average score of 77.60 (SD, ± 20.56) at 12 months.[81, level II-2] In another study involving 14 patients with primary or secondary dystonia treated with ITB, Walker et al. reported that of 14 patients with dystonia, five patients experienced improvement in symptoms (objective benefit) as determined by a change in rating scale scores, although only two had a clear clinical benefit. In patients with primary dystonia, seven out of nine patients had videotaped evidence to perform BFM ratings on and off ITB. Of these, decreased in BFM scores were seen in three patients. In patients with secondary dystonia, five patients had videotaped evidence to perform BFM ratings on and off ITB. Of these, two demonstrated objective clinical benefit.[84, level II-2]

b. Functional outcome

In the study by Motta et al. (2008), the second part of BFM scale evaluated the degree of disability. They found none of the patients showed any change regarding everyday activities because all patients studied belonged to GMFCS level V and so were affected by severe limitations in terms of autonomy and the need for assistance in everyday activities.[81, level II-2] Motta et al.(2009) reported significant improvement in both the dominant and the non dominant upper limbs ($P < 0.05$). The Melbourne Assessment Unilateral Upper Limb Function scale total percentage score for the dominant limb increased in all patients. The total average percentage score increased from baseline of 46.42 (SD, ± 19.6), to 55.44 (SD, ± 17.4) at 12 months. The total score for the non dominant limb improved in 10 of 11 patients and worsened in one case; the total average percentage score increased from 32.19 (SD, ± 18.9), to 40.61 (SD, ± 15) at 12 months.[82, level II-2]

Five studies evaluated the functional outcome based on subjective questionnaires. Motta et al. (2008) reported eighteen patients (95%) showed an improvement in the dystonias, whereas one (5%) exhibited no change. The caregivers reported an improvement in patient management (hygiene, dressing, feeding, and daily movement). Improvement in posture control and upper limb was also reported. Around half of the patients showed an improvement in sleeping (10 of 19 patients) and in mood (9 of 19 patients), whereas, 68% of caregivers reported no change in the area of autonomy.[81, level II-2] Parents perception of children change after treatment was sought through an interview at the follow-up. All caregivers reported improvements in patient management (i.e., hygiene, dressing, and daily movement) and improved posture and use of the upper limbs.[82, level II-2] Albright et al. conducted a telephone survey on the effect of ITB. Eighty five percent reported that the pump was 'worth it'. Quality of life and ease of care were considered to have improved in 86%. Speech was improved in 33%, swallowing in 26%, upper extremity function in 34%, and lower extremity function in 37% of the participants.[83, level II-2] Woom K, Tsegaye M, Vloeberghs MH conducted a cross sectional study in eight patients with dystonia who had ITB. The assessment regarding any improvement in general handling and posture were undertaken by the patient's carers. In all eight children, carers reported marked improvement in nursing care. In addition to reduction in spasticity and ease of nursing care, other benefits were noted; improved in sitting and sleeping, better control of head and arms, and less writhing movement. Improvement was most marked in children who had dystonia secondary to CP. Three patients who had both ITB and deep brain stimulation (DBS) insertion noticed synergistic improvement of both spasticity and functional component of dystonia.[85, level II-3] In a study by Ford et al., patients, family, and caretakers were asked whether they considered the ITB treatment had continuing beneficial effect on their quality of life. Six patients reported sustained benefit; however, in five other patients, the ITB had lost its effectiveness.[86, level II-2]

c. Satisfaction of treatment with continuous ITB infusion

Motta et al. (2008) reported that 15 out of 19 patients (79%) stated that they were satisfied with the implant and most (14 out of 19 patients) would do it again, three patients (16%) were not totally satisfied and were uncertain as to whether they would do it again, whereas one patient (5%) expressed dissatisfaction and would not undergo implant again and he chose to explant the pump four years after implant. Two out of 19 patients (11%) had the device removed: one due to dissatisfaction four years after the implant and another due to infection occurred 14 months after implant. [81, level II-2]

6.2.2. Safety of continuous ITB infusion for treatment of patients with severe dystonia

Six articles (studies) reported few complications or adverse events related to continuous ITB infusion for treatment of patients with severe dystonia. There were no deaths related to continuous ITB infusion reported in any of the studies.[81-86]

a. Drug related adverse events

Drug related adverse events were reported in four studies. Adverse events reported were constipation, loss of bowel and bladder control, decreased neck / trunk control, drowsiness, overdose, or withdrawal.[83-86] Moderate overdose was reported by Walker et al. in one out of 14 patients (7.1%).[84, level II-2] Ford et al. reported baclofen overdose with respiratory depression in four out of 25 patients (16.0%) and baclofen withdrawal in one out of 25 patients (4.0%).[86, level II-2]

b. Device related adverse events

Device related adverse events were reported in all the six studies. Catheter fracture, catheter rupture, CSF leaks, wound breakdown, wound dehiscence, alarm failure, infection, skin erosion were the commonly reported adverse events.[81-86]

6.3. SPASTICITY AND / OR DYSTONIA

Seven articles (studies) related to the effectiveness and safety of continuous ITB for treatment of patients with severe spasticity and / or dystonia met the inclusion criteria and included in this review. The included studies comprised of five pre- and post-intervention studies and two observational studies. There was no CEA / CUA of continuous ITB infusion for treatment of patients with severe spasticity and / or dystonia retrieved. The articles were published between 1999 and 2013. Two studies were conducted in the U.S.A, one in Japan, one in Australia, one in Italy, one in France, and one in Canada.

The total pooled sample size of all included studies was 297 subjects. Sample sizes of each of the included studies ranged from 17 to 139. The length of follow-up ranged from one month to 118 months.

Risk of bias

The pre- and post-intervention studies have clear and consistent inclusion and exclusion criteria in subject selection. Cross sectional studies have potentially higher risk of bias

6.3.1. Effectiveness of continuous intrathecal baclofen infusion for treatment of patients with severe spasticity and / or dystonia

a. Spasticity outcome

Five studies reported significant improvement in spasticity.[87-91, level II-2] Uchiyama et al. reported that lower limbs spasticity exhibited highly significant improvement regardless of catheter position while upper limbs spasticity exhibited more significant improvement when catheter was placed at the cervical spine. The mean AS scores for the affected lower limbs when the intrathecal catheter was placed at the lower thoracic spine level improved significantly from 3.07 to 1.69, $P < 0.0001$ and the mean AS scores for the affected lower limbs when the intrathecal catheter was placed at the cervical spine level in tetraplegia and dystonic patients improved significantly from 3.68 to 2.62, $P < 0.0001$. In the upper limbs, the mean AS scores for the affected upper limbs when the intrathecal catheter was placed at the lower thoracic spine level improved significantly from 2.87 to 2.30, $P < 0.004$ whereas, the mean AS scores for the affected upper limbs when the intrathecal catheter was placed at the cervical spine level in tetraplegia and dystonic patients improved significantly from 2.72 to 1.88, $P < 0.0001$.[87, level II-2] Motta F, Antonello CE, Stignani C reported reduction in AS score from a median of 3 [Interquartile range (IQR), 1] before the implant to a median value of 2 (IQR,1) at 12 months after the implant, $P < 0.001$.[88, level II-2] Ward et al. reported the median MAS score reduced significantly from 2.28 to 1.43, $P < 0.05$.[89, level II-2] Tasseel Ponche et al. reported a reduction in mean MAS score from 3.2 ± 0.4 points (range, 3 to 4) before initiation of therapy to 2.0 ± 0.6 points (range, 1 to 4) after therapy. [90, level II-2] Similarly, Meythaler et al. reported significant reduction in mean AS scores, mean SFS, and mean RS for both the upper and lower limbs. [91, level II-2]

b. Dystonia outcome

Two studies demonstrated improvement in dystonia. In the study by Motta F, Antonello CE, Stignani C the BAD score decreased from a median of 21 (IQR, 10) before the implant to a median value of 15 (IQR, 4) at 12 months after the implant, $P = 0.018$.[88, level II-2] Similarly, Ward et al. showed a reduction in BAD score from an average of 28.67 to 15.75, much greater than 25% improvement considered to be significant for this measurement tool.[89, level II-2]

c. Resting metabolic rate

Uchiyama et al. reported all 10 patients who underwent metabolic measurement exhibited resting hypermetabolism before the procedure, which declined after the procedure. Reduction was particularly marked in patients with dystonia and cerebral palsy, for whom metabolic rate had been over 1.5 times the normal value before surgery.[87, level II-2]

d. Functional outcome

The effects of continuous ITB infusion on motor function in individuals with spastic and dystonic CP was evaluated by Motta F, Antonello CE, Stignani C. The study found a significant improvement in the total median GMFM score in the overall population ($P < 0.001$) and in every dimension ($P < 0.05$), except for standing. The total median GMFM score was 65.66 (IQR, 49.61) before ITB increased to 70.33 (IQR, 43.86) at 12 months after ITB. The patients with severe impairment and those with mild to moderate impairment improved the total median GMFM score ($P < 0.001$ and $P < 0.05$, respectively). The best improvement in GMFM scores were reached by patients younger than 18 years. A subjective questionnaire administered to patients / caregivers revealed an overall improvement in participant functional abilities; 24 patients reported an improvement in transfer, 30 in care management, 25 in seat position, 31 in endurance, and 25 in walking. None of the assessed patients / caregivers reported worsening in the evaluated performance.[88, level II-2]

e. Goal attainment and satisfaction

Ward et al. conducted a study to determine whether continuous ITB infusion would lead to goal attainment. The patient's goals were measured with the Canadian Occupational Performance Measure (COPM) and goal attainment scaling (GAS). Each GAS goal was scaled from -2 to +2, with -2 being the least favourable outcome and +2 being the much greater than the expected outcome. The current level of performance was set at -1 and 0 was the expected outcome after ITB. The COPM has two domains; the performance and satisfaction with performance. Each domain was rated on a 0 to 10 rating scale, and a change in score of two or more was considered clinically significant. Overall, 16 subjects had a full data set with assessment of goals at baseline and goal attainment at six months post-implant. They found statistically significant increased in the satisfaction domain of COPM six months after implantation of baclofen pump; median of 2.1 (IQR, 1.76 to 2.75) at baseline increased to 5.9 (IQR, 4.86 to 7.05) at six months, difference 3.5 (IQR, 2.40 to 5.20, $P < 0.001$). Statistically significant increased in the performance domain; median of 2.2 (IQR, 2.00 to 2.70) at baseline increased to 5.4 (IQR, 4.6 to 6.9) at six months, difference 3.0 (IQR, 2.20 to 4.50, $P < 0.001$). The GAS was statistically higher at six months after implantation of baclofen pump: median of 35 at baseline compared with 56 (IQR, 47 to 65) at six months, difference 21(IQR, 12-30, $P < 0.001$). Seventy percent of the subjects attained their goals, having achieved a GAS score of 50 or over at six months.[89, level II-2]

In another study, Tasseel Ponche et al. subjectively assessed the efficacy of ITB in 25 wheelchair-dependent adults with CP using VAS. The pretherapeutic objectives were achieved when the patients reported an improvement of more than five out of 10 on the VAS. They reported in terms of the main objectives set prior to implantation, 96% of patients were seeking facilitated nursing and the mean satisfaction score was 6 ± 3.3 (range, 0 to 10). Eighty eight percent of patients were seeking improved wheelchair comfort and the mean satisfaction score was 6 ± 3 (range, 0 to 9). Twenty four percent of patients wanted a decrease in abnormal choreothetotic movement and the mean satisfaction score was 3 ± 4.1 (range, 0 to 8). Overall, 80% of the patients (n = 19) considered that their main ITB objectives have been achieved (VAS score greater than five out of 10). Furthermore, 88% of patients experienced improvement other than those wished for in the treatment objectives; pain relief in 68% of cases (15/22), easier movement execution in 45% of cases (10/22), and better sleep in 23% of cases (5/22). Better quality of life was reported in 72% of patients. The overall ITB satisfaction score was reported as 7 ± 3.2, with 80% of satisfied patients (VAS satisfaction score greater than five out of 10).[90, level II]

6.3.2. Safety of continuous intrathecal baclofen infusion for treatment of patients with severe spasticity and / or dystonia

Complications or adverse events related to continuous ITB infusion for treatment of patients with severe spasticity and / or dystonia were reported in six studies. There were no deaths related to continuous ITB infusion reported in any of the studies.[87-90,92-93] Most of the complications reported were device related adverse events such as catheter displacement, catheter fracture, CSF leak, or infection.[87-90, level II-2, 92, level II-3]

Ward et al. reported 0.38 complications per subject year of follow-up (i.e. approximately one complication for every 2.6 years of pump insertion). The complication rate was higher in children with dystonia (0.71) compared with those with spasticity (0.25), difference in rates was 0.46, P = 0.0017. The risk ratio of complication in children with dystonia compared with children with spasticity was 2.85 (CI: 1.36 to 6.08), P < 0.0034. In the spasticity predominant group, CSF leak was the most common problem at 27% (rate, 0.06 pump years) followed by infection and baclofen withdrawal (13% or a rate of 0.03 pump years each). In the dystonia-predominant group, infection was the most common at 22% (rate 0.16 pump years), followed by pump erosion (17% or rate of 0.12 pump years). There were high rates (0.08 per pump year) of procedure complications, catheter occlusions and excessive frequency of refills. Catheter problems were four times more likely in the dystonic group (rate of 0.12 per pump years), compared with the spastic group, (rate of 0.03 per pump year). Almost 50% of total complications occurred in the nine patients with dystonia.[89, level II-2] Tasseel Ponche et al. reported that complications occurred in 32% of the patients, with an overall rate of 0.07 complications / pump-year. Transient interruption of the treatment or surgical removal of the ITB pump was necessary in 16% of cases.[90, level II-2] Dickey et al. reported infectious complications of ITB in a paediatric population over a 15 year time period. Overall, 24 patients had 27 ITB device associated infections (10 after initial implantation and 17 after secondary ITB procedures). There were 2% superficial infections, 33% deep infections and 45% organ space infections. *Staphylococcus aureus* was isolated in 50% of those cultures obtained. Explantation was required in 59% of patients with an infection and differed by infection type; superficial (17%), deep (44%), and organ space (92%), P = 0.004.[92, level II-3]

Burn et al. conducted a retrospective chart and radiology review of all paediatric patients with baclofen pumps to assess the incidence of scoliosis. Cobb angles were measured preoperatively and on follow-up images. Thirty two patients were included in the study. The mean annual progression in Cobb angle in the entire group was 18.43° (range 0 to 67.68°, median 12.13°). The mean annual Cobb angle progression was similar in all four subgroups; CP, CP / dystonia, head injury, and others (range, 15.54° to 20.27°). Analysis of curve progression before and after growth spurt showed a greater rate of curve progression in patients with pumps inserted before the age of 15 years. Cobb angle progression per year (Mean ± SD); < 15 year (20° ± 20°/yr) and for ≥ 15 years (12°± 9°/yr).[93, level II-3]

6.4. ORGANIZATIONAL

Most of the studies were conducted in University Hospitals, Children Hospitals, Stroke Centres, Rehabilitation Hospitals, and MS Centres.[18-61] Effective treatment of spasticity and dystonia involved multidisciplinary team. It may include varying combinations of clinicians from neurologist, rehabilitation physician, physiotherapist, occupational therapist, neurosurgeon, psychiatrist, anaesthetist, nurse practitioner, orthopaedic surgeon and primary care practitioners.The team should be trained in ITB therapy.[15,36,50] Management of patients with baclofen pumps by experienced teams will help minimise serious complications.[63] As the implantable pumps require regular follow-up, monitoring, refilling and replacement once the battery expires, appropriate accessibility to specialised medical care is important, and patient and caregiver must be sufficiently motivated and capable of adhering to these requirements.[12] In a summary of NICE guidance for spasticity in children and young people with non-progressive brain disorders, it was stated to support those receiving ITB and their parents or carers by offering regular follow-up with the network team and a consistent point of contact with the specialist neurosurgical centre.[94]

Intrathecal baclofen withdrawal can be severe. Gooch et al. reported that family education has been critical in avoiding severe consequences of ITB withdrawal.[63] Krach LE, Nettleton A, Klempka B reported in a survey conducted among subjects or caregivers, approximately two third of 22 respondents mentioning about patient or caregiver education indicated that they would have benefited from additional education about the pump and its ongoing maintenance needs.[59] Taira et al. conducted a study to evaluate the incidence of complications of ITB therapy for spasticity in Japan where a unique training course and nationwide registration were required. An analysis of complications was performed in all patients who underwent ITB in Japan from 2005 to 2011. Prior to surgery, all doctors involved took a one-day training course, which included hands-on training. Surgical techniques that avoided complications were emphasised. They reported that the requirement of taking a training course before starting ITB seemed to reduce complications. Although there were surgery-related complications, the rate of complications in Japan appeared to be lower than those reported in larger series of ITB. However, whether the reported rates can be primarily ascribed to a mandatory training course requires further investigations.[66]

We calculated the potential direct cost (drugs, pump, and refill) of continuous ITB infusion for treatment of patients with severe spasticity or dystonia. This costing does not include cost for surgery and follow-up. (Communication with rehabilitation physician)

Cost for screening with injectable baclofen (Lioresal)

Test dose range from 25 mcg to 225 mcg
Cost of 50 mcg/ml injection = RM 150.00 / vial
Cost range = RM 150.00 to RM 750.00

Cost for continuous ITB infusion

Cost for drugs for continuous ITB infusion
Daily dose range from 300 mcg to 800 mcg
Total dose per annum range from 109.5 mg to 292 mg (365 days / year)
Cost of 10 mg/5ml or 10 mg/20 ml injection = RM 950.00
Cost per 1 mg = RM 95.00
Cost range = RM 10,402.50 to RM 27,740.00 per year

Cost for Synchromed II pump
Cost per unit = RM 36,000.00 (last for four to seven years depending on flow rate)
Cost range = RM 5,142.5 to RM 9,000.00 per year

Cost of refill kit
Cost per set = RM 85.00 / per set (usually refill every three to six monthly)
Cost range = RM 170.00 to RM 340.00 per year

Average cost per treated patient per annum (drugs + pump + refill kit)
Cost range = RM 15,715.00 to RM 37,080.00 over life span of the pump

7 DISCUSSION

There was no HTA report on continuous ITB infusion for treatment of patients with severe spasticity and dystonia. However, there was a HTA report on ITB pump for spasticity and a Cochrane protocol on ITB for treating spasticity in children with CP.[95-96] There is a substantial evidence based on 45 studies that continuous ITB infusion is effective in the treatment of patients with severe spasticity whose symptoms do not respond to oral and physical therapies, or who experience unacceptable side effects from oral baclofen. Most of the studies were pre- and post-intervention studies where patient's evaluation was done before and during follow-up at regular intervals after pump implantation. It should be noted that a higher level of evidence may be difficult to achieve due to ethical and logistic constraints associated with conducting controlled studies for long term treatment that involves invasive procedures and also for which the study population has been refractory to other forms of treatment. Several RCTs has also been conducted which provided evidence for the short term benefits of ITB.[18,20,22-25] The primary benefit of continuous ITB infusion is the relief of severe spasms and rigidity. From the studies included in this review, it was reported that the mean AS scores reduced from 2.8 – 4.6 at baseline (before treatment) to 0.4 – 2.6 at follow-up. The reduction in AS or MAS scores suggests that individual experienced less muscle rigidity as a result of receiving continuous ITB infusion.The mean SFS also reduced from 1.8 – 3.6 at baseline to 0.4 – 1.5 at follow-up, signifying that the average number of spasms endured per hour declined, and the reduction in RS substantiated improvement in spasticity. Pain associated with spasticity was also reduced.[18-19,25,29-31,33-34,38,45,55]

Reducing spasticity can improve overall function in daily activities. With the control of pain and spasticity, most children were able to extend their activities and participation.[19] Improvement in function was demonstrated as assessed by objective measures such as VAS, PEDI, GMFM, FIM/WeeFIM, BIS, and Melbourne Assessment of Unilateral Upper Limb Function. Improvement were reported for ease of care, self care, nursing care, social function, gross motor function which include mobility, cognitive function, caregiver assistance and upper limb function.[18-19,21,29,30,33-35,38,44,46-49] Significant improvement was also reported for gait and ambulation of post stroke spastic hypertonic patients and ambulant patients with severe spasticity.[46,48,54-56]

Many subjective functional improvements based on survey and observation were also reported such as improvement in daily activities, self care, transfers, ambulation, and ability to participate in activites.[21,23-24,32,41,49,59]

The efficacy of continuous ITB infusion was also manifested in an improved health related quality of life for patients with severe spasticity as assessed with CHQ-PF50, SIP, HSCL, SSQL, MSWS-12. Improved sleep, body pain and discomfort, body care and movement, increased independence and mental health enhances the quality of life.[18-19, 25,46-47,52,55] Four studies demonstrated that continuous ITB infusion improved quality of sleep.[30-31,57,58] Bensmail et al. postulated that reduction in spasms scores and reduction in periodic leg movement may have contributed to improve sleep continuity and sleep efficacy.[57] Treatment goals were fully met in 71% to 80% in three studies. Treatment goals were largely achieved in ease of care, improvement in function, and comfort.[27,40,59] Majority of patients and caregivers (80% to 90.5%) were satisfied with continuous ITB infusion and they would participate in the test treatment and implantation procedures again.[19,32,53,59] There was reduction in the average length of hospitalisation, and ITB therapy does not seemed to increase mortality in individuals with CP.[26,62] Reduction in muscle tone with continuous ITB infusion may slow or prevent the development of hip subluxation and dislocation in persons with CP.[60]

While pump implantation was well tolerated and there was no deaths reported, there were still a high number of drug or device related complications and adverse events. However, few patients had to discontinue treatment. Many adverse events such as infection, catheter malfunctioning, and seromas were easily resolved. These complications were reported to be tolerable in comparison with the relief in spasticity that the treatment brought. Drug holiday was found to be effective to treat drug tolerance.[26,28,31,71] Two studies with matched control group demonstrated that ITB has no significant effect on progression of scoliosis, while a study without a match control group demonstrated a significant increased in the rate of scoliotic curve progression after ITB pump placement when compared with published natural history data.[72-74]

Administration of continuous ITB infusion for treatment of patients with severe spasticity seemed to be cost-effective in the Netherlands, U.S.A, France and Japan based on their country willingness to pay threshold.[77-80] Based on the direct cost of the drug, pump, and refill kit, the estimated average cost per treated patient per annum range from RM 15,715.00 to RM 37,080.00 over life span of the pump. Despite the large upfront cost for the procedure, the long-term effects can be potentially money saving as demonstrated by Ordia et al. where reduction in hospital days represented an annual savings of $ 6,750 per patient and the cost of implanting the system would be paid back in less than two and half years on average.[26]

The evidence on the effectiveness and safety of continuous ITB infusion for patients with severe dystonia was much less compared to patients with severe spasticity. However, similar benefit of continuous ITB infusion was demonstrated. Continuous ITB infusion was found to be effective in improving dystonia, upper limb function, posture control, ease of care, patient management, and quality of life in patients with severe dystonia.[81-85] Drug and device related adverse events were also reported. However, there were no deaths associated with the use of continuous ITB infusion.[81-86] Significant improvement in spasticity, dystonia, resting metabolic rate, and motor function were reported by studies related to the effectiveness of continuous ITB infusion for treatment of patients with severe spasticity and / or dystonia.[87-91] Most of the complications reported were device related adverse events.[87-90] Complication rates were higher in children with dystonia (0.71 complications per subject year of follow-up) compared with those with spasticity (0.25 complications per subject year of follow-up), $P = 0.0017$.[89]

The complexity of the technology and patient population is reflected in the large number of trained professionals that is needed to provide an effective management team. Because patients with severe spasticity and / or dystonia suffer long-term consequences, the effect of continuous ITB infusion must be monitored. Family and caregiver education about the pump and its maintenance would be beneficial to avoid adverse consequences related to baclofen overdose or withdrawal.

Limitations

The systematic review of literature has several limitations. There were limited long term studies conducted on continuous ITB infusion that included control group. Most of the studies were pre- and post-intervention studies with series of measurement before and after pump implantation. There is no checklist for assessment of risk of bias for pre- and post-intervention study in CASP. However, according to Methods for the development of NICE public health guidance (third edition), a good quality of pre-post study will demonstrate clear and consistent inclusion and exclusion criteria in subject selection and causality between intervention and outcome will often be strengthened when observed changes are significant and occur soon after intervention.[97] Generalizability and international comparisons of economic evaluations are very limited. Although there was no restriction in language during the search but only English full text articles were included in the report.

8 CONCLUSION

There was substantial fair level of retrievable evidence to suggest that continuous ITB infusion was effective in reducing spasticity, reducing pain, improved function and quality of life in patients with severe spasticity who were unresponsive or cannot tolerate oral baclofen. Majority of the treatment goals were attained. Patients and caregivers were satisfied with the treatment. Although there was the risk of adverse events related to continuous ITB infusion, the treatment is considered relatively safe, minimally invasive and reversible. Continuous ITB infusion for treatment of patients with severe spasticity seemed to be cost-effective in some countries.

There was limited fair level of retrievable evidence to suggest that continuous ITB infusion was also safe and effective in reducing dystonia, reducing spasticity, improved function and quality of life in patients with severe dystonia or having both spasticity and dystonia who were unresponsive or cannot tolerate oral baclofen. Complication rates were higher in children with dystonia compared with those having spasticity. There was no retrievable evidence on the cost-effectiveness of continuous ITB infusion for treatment of patients with severe dystonia or having both spasticity and dystonia.

This treatment system requires long term monitoring by an experienced healthcare team. Besides proper training for the healthcare teams, patients and caregivers education has been critical in avoiding severe consequences of ITB withdrawal. The estimated average cost per treated patient per annum (drugs, pump and refill kit) range from RM 15,715.00 to RM 37,080.00 over life span of the pump. However, long-term effects can be potentially money saving.

9 RECOMMENDATION

Continuous ITB infusion may be utilised in patients with severe spasticity or severe dystonia or having both conditions who are unresponsive or cannot tolerate oral baclofen, by trained multidisciplinary healthcare teams. Criteria for patient selection should be developed. Records of patients on continuous ITB infusion should be maintained by the treating physicians. Patient's outcome research is warranted on a long term basis.

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Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2
PTK – FM – 02

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
CONTINUOUS INTRATHECAL BACLOFEN (ITB) INFUSION FOR SEVERE SPASTICITY AND DYSTONIA

1. BACKGROUND INFORMATION

Spasticity refers to an abnormal, velocity-dependent increase in muscle tone resulting from interruption of the neural circuitry regulating the muscles and is a common complication of cerebral palsy (CP), brain injuries, spinal cord injury (SCI), multiple sclerosis (MS) and stroke. The muscle stretch reflex is thought to play an important role in spasticity generation. Spasticity can cause pain, decreased range of motion, gait problems, contractures, decubitus ulcers, and pressure sores, which in turn lead to decreased independence, functioning, and quality of life. In a study conducted among 27 CP patients attending the Paediatric Rehabilitation Clinic at University of Malaya Medical Centre, 11.1% patients reported severely affected quality of life, 25.9% patients reported moderately affected quality of life and 37% reported mildly affected quality of life. Spasticity can have a significant detrimental effect on daily functions, such as feeding, dressing, hygiene, bladder and bowel control, and mobility; patients' need for support can also influence the cost of care. Dystonia is characterised by sustained muscle contractions that cause twisting and repetitive movements and abnormal postures. Dystonia has been classified as primary, primary plus, secondary, and heredo-degenerative. Secondary dystonia is perhaps the most common type due to its association with two frequent conditions: CP and traumatic brain injury. Secondary dystonia is typically generalised and causes progressive disability, discomfort, and deformity.

In a systematic review and meta-analysis of 49 studies, Oskoui et al. reported that the pooled overall prevalence of CP was 2.11 per 1,000 live births (95% confidence interval:1.98 to 2.25). In Malaysia, the estimated prevalence of MS is one to two per 100,000 population. The incidence of spinal injuries in Malaysia is on the rise following similar trend of rapid development and increasing number of building constructions sites, and motor vehicles. A retrospective study conducted in the Spinal unit, Department of Orthopaedics and Traumatology, University Kebangsaan Malaysia Medical Centre (UKMMC) found that motor vehicle accidents were identified as the leading cause of SCI (39%). Of the complications cited, bladder and bowel problems were the most frequent (65%), followed by spasticity (27.3%) and pressure ulcer (26%).

The usual approach to treating spasticity relies on trying to decrease muscle tone with physical exercises and medication (baclofen, dantrolene sodium, diazepam, clonidine) used as monotherapy or in combination. More recently, new medications have been proposed (tizanidine, cannabinoid, 4-aminopyridine, botulinum toxin), as well as older drugs (i.e. baclofen) via new administration routes such as an implanted intrathecal pump. Intrathecal baclofen (ITB) is variously referred to as intrathecally-administered baclofen, intrathecal baclofen infusion, and continuous baclofen infusion.

For patients with spinal spasticity, their response to oral medication is often poor and before intrathecal infusion, the alternative was destructive surgery that either cut nerve roots or disrupted spinal-cord circuits. Intrathecal delivery methods have been developed as an alternative to chronic systemic administration in an attempt to reduce pharmacological side effects such as physical tolerance, psychological dependency, and neurotoxicity. Oral medications used to treat dystonia include baclofen, clonazepam, trihexyphenidyl, and levo-dopa. In general, oral medications diminish dystonia in minority of participants and cause dramatic improvement in even fewer. The use of ITB for dsytonia was reported in 1991.

Baclofen, an agonist of the inhibitory neurotransmitter γ-aminobutryric acid (GABA), is currently the most widely used antispasmodic drug for treatment of spasticity. Baclofen acts at the level of the spinal cord to inhibit calcium uptake, which, in turn, impedes the release of excitatory neurotransmitters that play a role in spasticity. Physiologic studies suggest that baclofen acts presynaptically to reduce motor neuron excitability by inhibiting the release of excitatory neurotransmitters. At higher cerebrospinal fluid concentrations, baclofen may also act postsynaptically to antagonize the actions of excitatory neurotransmitters. Baclofen has poor lipid solubility and does not cross the blood-brain barrier effectively. Therefore, even at large doses, oral baclofen reaches relatively low levels at its site of action in the cerebrospinal fluid, thus providing limited inhibition of spasticity. At the same time, high plasma levels of baclofen resulting from oral administration can produce unwanted side-effects of the central nervous system such as sedation, somnolence, and ataxia, as well as respiratory and cardiovascular depression.

In contrast, in continuous ITB infusion, the baclofen is directly infused into the intrathecal space and acts directly on the GABA receptor sites in the spinal cord. Patients receiving baclofen via a constant intrathecal infusion (400 µg/day) have cerebrospinal fluid levels of 380 ng/ml, as compared to the much lower levels (<12-95 ng/ml) seen with oral baclofen administration. In addition, serum baclofen level is very low (< 5 ng/ml) when the drug is administered intrathecally. Thus, as compared with oral administration of baclofen, intrathecal delivery produces cerebrospinal fluid levels at least four-times higher with 1/100th of the systemic dose and 1/100th the plasma level.

This relatively high ratio of cerebrospinal-to-plasma drug level, combined with the facts that intrathecal administration concentrates baclofen at appropriate receptor sites in the spinal cord and results in 4:1 ratio of drug concentration between lumbar and cervical regions of the spine, accounts for both the efficacy and relatively low levels of CNS-related side effects associated with intrathecal administration.

The continuous ITB infusion system consists of a catheter and a pump. The pump is surgically placed under the skin of the abdomen near the waistline, under general anaesthesia. The pump stores and releases prescribed amounts of medication through the catheter. The pump is refilled by inserting a needle through the skin into a filling port in the centre of the pump. Pumps can be programmable or non-programmable, depending on the type of medication delivery required. Programmable pumps are for flexible medication delivery as dose titration and regulation will vary due to the dynamic nature of pain, and non-programmable pumps are for fixed rate medication delivery when the dosage is expected to be stable. Using an external programmer, a physician can make adjustments in the dose, rate and timing. The pump reservoir can be refilled approximately every two to three months by percutaneous injection. The pump is taken out and replaced at the end of the battery's life span (approximately five to seven years). Claimed advantages of ITB therapy are:

i. Direct drug administration to the CSF
   - Minimized the central side effects of oral baclofen
   - Concentrates the drug in the CSF at higher levels than via the oral route
   - Intrathecal administration can use concentrations of baclofen of less than one hundredth of those used orally

ii. Adjustable / programmable continuous infusion make it possible to titrate the doses and vary doses suitable for daily activities

iii. Reversible (in contrast to surgery)

Intrathecal baclofen is indicated in patients with severe spasticity uncontrolled by conventional treatment or who experienced intolerable side effects to oral baclofen.

The goals of treatment are:

- Decrease spasticity
- Decrease pain
- Facilitate movement and mobility
- Reduce energy expenditure
- Improve quality of life
- Reduce secondary musculoskeletal complications

Continuous ITB infusion has not been practised in any government hospital in Malaysia. Therefore, there is a need to assess the feasibility of using continuous ITB infusion for treatment of patients with severe spasticity or dystonia or both. This HTA was requested by Rehabilitation Physicians, Hospital Raja Permaisuri Bainun, Ipoh, Perak.

2. POLICY QUESTION

In Ministry of Health Facilities, should continuous ITB infusion be used for treatment of patients with severe spasticity or dystonia or having both conditions who were uncontrolled by conventional treatment?

3. OBJECTIVE

3.1 To assess the safety of continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions compared with conventional treatment.

3.2 To assess the effectiveness of continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions compared with conventional treatment.

3.3 To assess the economic implications of using continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions compared with conventional treatment.

3.4 To assess the organizational issues related to the use of continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions compared with conventional treatment.

Research questions

I. How safe is continuous ITB infusion compared with conventional treatment?

II. What are the short and long term benefits of using continuous ITB infusion compared with conventional treatment for patients with severe spasticity or dystonia or having both conditions?

III. What is the economic implication of using continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions?

IV. What are organizational issues related to the use of continuous ITB infusion for treatment of patients with severe spasticity or dystonia or having both conditions?

4. METHODS

4.1. Search Strategy

4.1.1 Electronic database will be searched for published literatures pertaining to the use of ITB therapy for treatment of patients with severe spasticity or dystonia.

4.1.2 Databases as follows: MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database and Embase through the Ovid interface. Searches will also be conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database.

4.1.3 Additional literatures will be identified from the references of the retrieved articles.

4.1.4 General search engine will also be used to get additional web-based materials and information.

4.1.5 The detail of the search strategy will be presented as appendix.

4.2. Inclusion and exclusion criteria

4.2.1. Inclusion criteria

a. Population : Patients with spasticity or dystonia or having both conditions (adult and children).
b. Intervention : Continuous ITB infusion.
c. Comparators : Conventional treatment (oral medication, injection, physical therapy,rhizotomy) or placebo / no comparator
d. Outcome:
- Adverse events – drug or device related
- Severity of spasticity
- Pain
- Severity of dystonia
- Frequency and severity of spasm
- Quality of life (patient and carers)
- Functional outcome – mobility, activity of daily living, participation
- Hospitalisation – admission, length of stay
- Reduction of secondary complication due to spasticity (e.g. contraction, pressure ulcer)
- Economic evaluation
- Organizational issues – operational, training, resources

e. Study design: HTA report, Systematic Review, Randomised Controlled Trials (RCT), Non Randomised Controlled Trial, Observational studies (Cohort, Case-control, Pre and post intervention studies, cross sectional studies), and studies which include economic evaluation.

f. Full text articles published in English

4.2.2 Exclusion criteria

a. Study design : Animal study, laboratory study, narrative review, editorials, letter to the editors, case reports
b. Non English full text article.

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Data extraction strategy

The following data will be extracted:

4.3.1 Details of methods and study population characteristics.

4.3.2 Details of intervention and comparators.

4.3.3 Details of individual outcomes: safety, effectiveness, cost implication, organizational and societal issues associated with the use of ITB therapy.

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form. Disagreements will be resolved by discussion.

4.4 Quality assessment strategy

The risk of bias (methodology quality) of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) by two reviewers depending on the type of the study design.

4.5 Methods of analysis/synthesis

Data on the safety, effectiveness and cost implication of using ITB will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5 REPORT WRITING

Appendix 3

SEARCH STRATEGY

MEDLINE ® In progress and other Non-Indexed Citations and Ovid Medline® 1946 to present.

1. Muscle spasticity/
2. (muscle adj1 spastic*).tw.
3. spastic*.tw.
4. Spasm/
5. (Spasm* adj1 (muscular or ciliary body or muscle or generalized)).tw.
6. Spasm*.tw.
7. Spinal Cord Injuries/
8. (spinal cord adj1 (injur* or contusion or traum* or laceration*)).tw.
9. (spinal adj1 (cord traum* or cord injur* or cord contusion*)).tw.
10. Cerebral Palsy/
11. (spastic* adj diplegia*).tw.
12. (cerebral pals* adj1 (hypotonic or monoplegic or athetoid or quadriplegic infantile or monoplegic infantile or atonic or spastic* or dyskinetic or congenital or mixed or dystonic rigid or dystonic-rigid or diplegic infantile or rolandic type)).tw.
13. cp.tw.
14. cerebral palsy.tw.
15. (Infantile cerebral palsy adj1 (quadriplegic or diplegic or monoplegic)).tw.
16. brain injuries/
17. (injur* adj1 (traum* brain or mild traum* brain or brain traum* mild or diffuse brain or focal brain or acute brain or brain)).tw.
18. (brain injur* adj1 (traum* or acute or focal or diffuse)).tw.
19. (encephalopath* adj1 (post concussive or post-concussive or traum* or post-traum* or post traum*)).tw.
20. (brain adj1 (traum* or laceration* or contusion*)).tw.
21. (cortical adj1 contusion*).tw.
22. traumatic brain injury.tw.
23. tbi*.tw.
24. Diffuse Axonal Injury/
25. (injur* adj1 diffuse axonal).tw.
26. dai*.tw.
27. diffuse axonal injury.tw.
28. axonal injur* diffuse.tw.
29. BRAIN HEMORRHAGE, TRAUMATIC/
30. (h?emorrhage* adj1 (traumatic cerebellar or traumatic brain)).tw.
31. (traum* adj1 (cerebellar h?emorrhage* or brain h?emorrhage*)).tw.
32. brain stem hemorrhage, traumatic/
33. (traum* adj1 (brainstem h?em* or brain stem h?em* or bulbar h?em* or
34. medullary h?em* or pontine h?em* or midbrain h?em* or h?em* brain stem or
35. h?em* brainstem)).tw.
36. (h?em* adj1 (traumatic medullary or traumatic bulbar or post-traumatic brainstem)).tw.
37. cerebral hemorrhage, traumatic/
38. (traum* adj1 (cerebral h?em* or intracerebral h?em* or cerebral parenchymal h?em* or brain h?em* cerebral or cerebral intraparenchymal h?em*)).tw.
39. (h?em* traum* adj1 (intracerebral or cerebral)).tw.
40. Multiple Sclerosis/
41. (disseminated adj1 sclerosis).tw.
42. ms.tw.
43. multiple sclerosis.tw.
44. Multiple Sclerosis, Chronic Progressive/
45. (multiple sclerosis adj1 (secondary progressive or primary progressive or progressive relapsing or chronic progressive or remittent progressive)).tw.
46. Stroke/
47. (Stroke* adj1 (cerebr* or acute)).tw.
48. (cerebrovascular adj1 (apoplexy or accident acute or accident*)).tw.
49. (Brain adj1 vascular accident*).tw.
50. cva*.tw.
51. cerebrovascular accident.tw.
52. stroke*.tw.
53. acute cerebrovascular accident*.tw.
54. Dystonia/
55. (dystonia adj1 (paroxysmal or limb or muscle or diurnal)).tw.
56. dystonia.tw.
57. Hypoxia, Brain/
58. (anoxi* adj1 (encephalopath* or brain damage or brain or cerebral)).tw.
59. (Hypoxi* adj1 (brain or encephalopath* or cerebral or brain or brain damage)).tw.
60. Hypoxia-Ischemia, Brain/
61. ((Brain or cerebral or encephalopath*) adj1 (isch?emia*- anoxi* or isch?emia* anoxi* or isch?emia* hypoxia or isch?emia*- hypoxi* or hypoxia*-isch?emia*or hypoxi* isch?emia*)).tw
62. acquired brain injury.tw.
63. or/1-60
64. Baclofen.tw.
65. Lioresal.tw
66. Gablofen.tw.
67. Baclosan.tw.
68. (injection* adj1 (intrathecal or intraspinal or spinal)).tw.

69. Baclofen/
70. Injections, Spinal/
71. Muscle Relaxants, Central/
72. (muscle relaxant* adj1 (central or centrally acting)).tw.
73. Infusion Pumps, Implantable/
74. drug delivery systems implantable.tw.
75. (implantable adj1 (infusion pump* or peristaltic pump* or perfusion pump*)).tw
76. 62 or 63 or 64 or 65 or 67 or 69 or 70
77. 66 or 68 or 71 or 72 or 73
78. 74 AND 75
79. Baclofen/
80. Lioresal.tw
81. Gablofen.tw.
82. Baclosan.tw.
83. Administration, Oral/
84. (oral adj1 (drug administration* or administration*)).tw.
85. Dantrolene/
86. (dantrolene adj1 sodium).tw.
87. dantrolene.tw
88. dantrium.tw.
89. Diazepam/
90. Diazepam.tw.
91. Valium.tw.
92. Cannabinoids/
93. Cannabinoids.tw.
94. 4-Aminopyridine/
95. 4 aminopyridine.tw.
96. 4-aminopyridine.tw.
97. Pymadine.tw.
98. Botulinum Toxins/
99. (botulinum adj1 toxin*).tw.
100. botulin.tw.
101. BTX.tw.
102. BoNT.tw.
103. Botox.tw.
104. Exercise/
105. (exercise* adj1 (isometric or aerobic or physical)).tw.
106. exercise*.tw.
107. physical therapy.tw.
108. muscle stretching exercises/
109. (stretching adj1 (exercise muscle or static active or static-active or static passive or static-passive or passive or active or static or dynamic or relaxed or isometric)).tw.
110. Phenols/
111. Phenol*.tw.
112. Injections, Spinal/
113. (injection* adj1 (intrathecal or intraspinal or spinal)).tw.
114. 108 or 109
115. 110 or 111
116. 112 and 113
117. Rhizotomy/
118. Rhizotom*.tw.
119. Dorsal rhizotom*.tw.
120. Placebo Effect/
121. (placebo adj1 effect*).tw.
122. 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 114 or 115 or 116 or 117 or 118 or 119
123. 61 and 74 and 75 and 120

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1. (muscle adj1 spastic*).tw.
2. spastic*.tw.
3. muscle spasticity.tw.
4. (Spasm* adj1 (muscular or ciliary body or muscle or generalized)).tw.
5. Spasm*.tw.
6. (spinal cord adj1 (injur* or contusion or traum* or laceration*)).tw.
7. (spinal adj1 (cord traum* or cord injur* or cord contusion*)).tw.
8. Spinal Cord Injuries.tw.
9. (spastic* adj diplegia*).tw.
10. (cerebral pals* adj1 (hypotonic or monoplegic or athetoid or quadriplegic infantile or monoplegic infantile or atonic or spastic* or dyskinetic or congenital or mixed or dystonic rigid or dystonic-rigid or diplegic infantile or rolandic type)).tw.
11. cp.tw.
12. cerebral palsy.tw.
13. (Infantile cerebral palsy adj1 (quadriplegic or diplegic or monoplegic)).tw.
14. (injur* adj1 (traum* brain or mild traum* brain or brain traum* mild or diffuse brain or focal brain or acute brain or brain)).tw.
15. (brain injur* adj1 (traum* or acute or focal or diffuse)).tw.
16. (encephalopath* adj1 (post concussive or post-concussive or traum* or post-traum* or post traum*)).tw.
17. (brain adj1 (traum* or laceration* or contusion*)).tw.
18. traumatic brain injury.tw.
19. tbi*.tw.

20. BRAIN INJURIES.tw.
21. (injur* adj1 diffuse axonal).tw.
22. dai*.tw.
23. diffuse axonal injury.tw.
24. axonal injur* diffuse.tw.
25. (h?emorrhage* adj1 (traumatic cerebellar or traumatic brain)).tw.
26. (traum* adj1 (cerebellar h?emorrhage* or brain h?emorrhage*)).tw.
27. BRAIN HEMORRHAGE, TRAUMATIC.tw.
28. (traum* adj1 (cerebral h?em* or intracerebral h?em* or cerebral parenchymal h?em* or brain h?em* cerebral or cerebral intraparenchymal h?em*)).tw.
29. (h?em* traum* adj1 (intracerebral or cerebral)).tw.
30. CEREBRAL HEMORRHAGE, TRAUMATIC.tw.
31. ms.tw.
32. multiple sclerosis.tw.
33. (multiple sclerosis adj1 (secondary progressive or primary progressive or progressive relapsing or chronic progressive or remittent progressive)).tw.
34. Multiple Sclerosis, Chronic Progressive.tw.
35. (Stroke* adj1 (cerebr* or acute)).tw.
36. (cerebrovascular adj1 (apoplexy or accident acute or accident*)).tw.
37. cva*.tw.
38. cerebrovascular accident.tw.
39. acute cerebrovascular accident*.tw.
40. (dystonia adj1 (paroxysmal or limb or muscle or diurnal)).tw.
41. dystonia.tw.
42. (anoxi* adj1 (encephalopath* or brain damage or brain or cerebral)).tw.
43. (Hypoxi* adj1 (brain or encephalopath* or cerebral or brain or brain damage)).tw.
44. Hypoxia, Brain.tw.
45. ((Brain or cerebral or encephalopath*) adj1 (isch?emia*- anoxi* or isch?emia* anoxi* or isch?emia* hypoxia or isch?emia*- hypoxi* or hypoxia*-isch?emia*or hypoxi* isch?emia*)).tw.
46. Hypoxia-Ischemia, Brain.tw.
47. acquired brain injury.tw.
48. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. Baclofen.tw.
50. Lioresal.tw.
51. Baclosan.tw.
52. (muscle relaxant* adj1 (central or centrally acting)).tw.
53. 49 or 50 or 51 or 52
54. (implantable adj1 (infusion pump* or peristaltic pump* or perfusion pump*)).tw.
55. Infusion Pumps, Implantable.tw.
56. 54 or 55
57. 48 and 53 and 56

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(Muscle spasticity[MeSH Terms]) OR muscle spasticity[Title/Abstract]) OR spastic*[Title/Abstract]) OR spasticism[MeSH Terms]) OR spasm[MeSH Terms]) OR Spasm*[Title/Abstract]) OR Muscl* Spasm*[Title/Abstract]) OR Generalized Spasm*[Title/Abstract]) OR spinal cord injury[MeSH Terms]) OR Spinal Cord Trauma*[Title/Abstract]) OR Spinal Cord Injur*[Title/Abstract]) OR Traumatic Myelopath*[Title/Abstract]) OR Spinal Cord Transection*[Title/Abstract]) OR Spinal Cord Laceration*[Title/Abstract]) OR Post-Traumatic Myelopath*[Title/Abstract]) OR Spinal Cord Contusion*[Title/Abstract]) OR cerebral palsy[MeSH Terms]) OR CP (Cerebral Palsy)[Title/Abstract]) OR Dystonic-Rigid Cerebral Palsy[Title/Abstract]) OR Mixed Cerebral Pals*[Title/Abstract]) OR Monoplegic Infantile Cerebral Palsy[Title/Abstract]) OR Quadriplegic Infantile Cerebral Palsy[Title/Abstract]) OR Spastic Diplegia*[Title/Abstract]) OR Monoplegic Cerebral Pals*[Title/Abstract]) OR Athetoid Cerebral Pals*[Title/Abstract]) OR Dyskinetic Cerebral Pals*[Title/Abstract]) OR Atonic Cerebral Pals*[Title/Abstract]) OR Hypotonic Cerebral Pals*[Title/Abstract]) OR Diplegic Infantile Cerebral Pals*[Title/Abstract]) OR Spastic Cerebral Pals*[Title/Abstract]) OR brain injury[MeSH Terms]) OR Brain Injur*[Title/Abstract]) OR Diffuse Focal Brain Injur*[Title/Abstract]) OR Traumatic Brain Injur*[Title/Abstract]) OR Brain Trauma*[Title/Abstract]) OR Traumatic Brain Injur*[Title/Abstract]) OR TBI (Traumatic Brain Injury)[Title/Abstract]) OR TBIs (Traumatic Brain Injury)[Title/Abstract]) OR TBI*[Title/Abstract]) OR Brain Laceration*[Title/Abstract]) OR Brain Contusion*[Title/Abstract]) OR Post Traumatic Encephalopath*[Title/Abstract]) OR Post-Traumatic Encephalopath*[Title/Abstract]) OR Post Concussive Encephalopath*[Title/Abstract]) OR Acute Brain Injur*[Title/Abstract]) OR multiple sclerosis[MeSH Terms]) OR Disseminated Sclerosis[Title/Abstract]) OR MS (Multiple Sclerosis)[Title/Abstract]) OR Multiple Sclerosis, Chronic Progressive[MeSH Terms]) OR Chronic Progressive Multiple Sclerosis[Title/Abstract]) OR Remittent Progressive Multiple Sclerosis[Title/Abstract]) OR Progressive Relapsing Multiple Sclerosis[Title/Abstract]) OR Secondary Progressive Multiple Sclerosis[Title/Abstract]) OR Primary Progressive Multiple Sclerosis[Title/Abstract]) OR Stroke[MeSH Terms]) OR Strokes[Title/Abstract]) OR CVA* (Cerebrovascular Accident)[Title/Abstract]) OR Cerebrovascular Accident*[Title/Abstract]) OR Cerebrovascular Apoplexy Cerebrovascular[Title/Abstract]) OR Stroke*[Title/Abstract]) OR Brain Vascular Accident*[Title/Abstract]) OR Cerebral Stroke*[Title/Abstract]) OR Acute Stroke*[Title/Abstract]) OR Acute Cerebrovascular Accident*[Title/Abstract])) AND (((((((((Baclofene[Title/Abstract]) OR Lioresal[Title/Abstract]) OR Kemstro[Title/Abstract]) OR Liofen[Title/Abstract]) OR Gablofen[Title/Abstract]) OR Beklo[Title/Abstract]) OR Baclosan[Title/Abstract])) AND ((((((((((Injections, Spinal) OR Intraspinal Injection*[Title/Abstract]) OR njection* Spinal[Title/Abstract]) OR Intrathecal Injection*[Title/Abstract]) OR Infusion Pumps, Implantable[MeSH Terms]) OR Implantable Perfusion Pump*[Title/Abstract]) OR Implantable Infusion Pump*[Title/Abstract]) OR Programmable Implantable Medication Systems*[Title/Abstract]) OR Implantable Peristaltic Pump*[Title/Abstract]))

Appendix 4

SUMMARY OF CASP CHECKLIST

SYSTEMATIC REVIEW

CRITERIA ASSESSED			
Selection of studies (relevant studies included?)	Yes ☐	No ☐	Can't tell ☐
Assessment of quality of included studies?	Yes ☐	No ☐	Can't tell ☐
If the results of the review have been combined, is it reasonable to do so? (heterogeneity)	Yes ☐	No ☐	Can't tell ☐

RCT

CRITERIA ASSESSED			
Assignment of patients randomised?	Yes ☐	No ☐	Can't tell ☐
Allocation concealment?	Yes ☐	No ☐	Can't tell ☐
Patients, health workers, study personnel blind to treatment?	Yes ☐	No ☐	Can't tell ☐
Intention to treat analysis?	Yes ☐	No ☐	Can't tell ☐
Explanation of loss to follow-up?	Yes ☐	No ☐	Can't tell ☐

COHORT

CRITERIA ASSESSED			
Selection (cohort recruited in an acceptable way?)	Yes ☐	No ☐	Can't tell ☐
Exposure accurately measured?	Yes ☐	No ☐	Can't tell ☐
Outcome accurately measured?	Yes ☐	No ☐	Can't tell ☐
Confounding factors identified and taken account?	Yes ☐	No ☐	Can't tell ☐
Follow-up of subjects complete and long enough?	Yes ☐	No ☐	Can't tell ☐

CASE- CONTROL

CRITERIA ASSESSED			
Selection (cases and control recruited in an acceptable way?)	Yes ☐	No ☐	Can't tell ☐
Exposure accurately measured?	Yes ☐	No ☐	Can't tell ☐
Confounding factors identified and taken account?	Yes ☐	No ☐	Can't tell ☐

ECONOMIC EVALUATION

CRITERIA ASSESSED			
A well-define question posed?	Yes ☐	No ☐	Can't tell ☐
Comprehensive description of competing alternative given?	Yes ☐	No ☐	Can't tell ☐
Effectiveness established?	Yes ☐	No ☐	Can't tell ☐
Effects of intervention identified, measured and valued appropriately?	Yes ☐	No ☐	Can't tell ☐
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	Yes ☐	No ☐	Can't tell ☐
Costs and consequences adjusted for different times at which they occurred (discounting)?	Yes ☐	No ☐	Can't tell ☐
Results of the evaluation?	Yes ☐	No ☐	Can't tell ☐
Incremental analysis of the consequences and costs of alternatives performed?	Yes ☐	No ☐	Can't tell ☐
Sensitivity analysis performed?	Yes ☐	No ☐	Can't tell ☐

Appendix 5

ASSESSMENT TOOLS

Rating Scales	Description
Ashworth Scale	
1	No increase in tone
2	Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension
3	More marked increase in tone, but affected part easily flexed
4	Considerable increase in tone; passive movement difficult
5	Affected part rigid in flexion or extension
Modified Ashworth Scale	
0	No increase in tone
1	Slight increase in tone, manifested by a catch and release or by minimal resistance at the end of the movement
2	Slight increase in muscle tone, manifested by a catch, followed by a minimal resistance throughout the remainder (less than half) of the range of movement (ROM)
3	More pronounced increase in tone through most of the ROM, but affected part easily flexed
4	Considerable increase in tone; passive movement difficult
5	Affected part rigid in flexion or extension
Spasm Frequency Score	
0	No spasms
1	Mild spasms induced by stimulation
2	Infrequent full spasms occurring less than once per hour
3	Spasms occurring more than once per hour
4	Spasms occurring more than 10 times per hour
Reflex Score	
0	Reflexes absent
1	Hyporeflexia
2	Normal
3	Mild hyperreflexia
4	3 or 4 beats clonus only
5	Clonus
Gillette Functional Assessment Questionnaire	
1	Cannot take any steps at all
2	Can do some stepping on his / her own with the help of another person Does not take full weight on feet, does not walk on routine basis
3	Walks for exercise in therapy and less than typical household distances. Usually requires assistance from another person.
4	Walks for household distances, but makes slow progress. Does not use walking at home as preferred mobility (primarily walks in therapy).
5	Walks more than 15-50 feet but only inside at home or school (walks for household distances)
6	Walks more than 15-50 feet outside the home, but usually uses a wheelchair or stroller for community distances or congested areas
7	Walks outside the home for community distances, but only on level surfaces (cannot perform curbs, uneven terrain, or stairs without assistance of another person
8	Walks outside the home for community distances, is able to perform curbs and uneven terrain in addition to level surfaces, but usually requires minimal assistance or supervision for safety
9	Walks outside the home for community distances, easily gets around on level ground, curbs, and uneven terrain, but has difficulty or requires minimal assistance with running, climbing, and / or stairs. Has some difficulty keeping up with peers.
10	Walks, runs, and climbs on level and uneven terrain without difficulty or assistance

Appendix 6

SPASTICITY

Evidence Table : EFFECTIVENESS

Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	1. Hoving MA, van Raak E P.M, Spincemaille GHJJ, Palmans LJ, Becher JG, Vles JSH. Efficacy of intrathecal baclofen therapy in children with intractable spastic cerebral palsy: A randomised controlled trial. European Journal of Paediatric Neurology. 2009;13:240-246.
Study Type / Methods	Randomised controlled trial conducted at the University Hospital Maastricht in the Netherlands. The aim of this RCT was to study the efficacy of continuous infusion of intrathecal baclofen (CITB) in the treatment of children with problems caused by intractable spastic cerebral palsy (CP). After successful test treatment phase (n=17), the children were randomised to receive a programmable infusion pump (Medtronic, Inc., Minneapolis, MN) after either 1 month (CITB group) or 6 months (Control group). In both groups, standard treatment was continued, including any physiotherapy, speech therapy and occupational therapy. Before the start of the study, an independent statistician generated the allocation schedule with an unpredictable sequence of assignments. The investigator who enrolled the children had no entry to this list and was, at the time of enrolment, not aware of the next assignment in the sequence. For assignment, the investigator called the independent statistician who consulted the allocation list. After randomisation, the treatment was open-label and non-blinded. An experienced neurosurgeon inserted the pumps under general anaesthesia in the lateral abdomen. All children participated in the 3 monthly follow-up visits. The main investigator was present during all admissions and follow-up visits of the children. Outcomes measures: Compared 6 months change scores between the CITB group and the Control group. Two primary outcome measures: • Caregiver assistance scale of the self-care domain of the Paediatric Evaluation of Disability Inventory (PEDI) • Visual analogue scale (VAS) for the individually formulated problems. VAS is a 10-cm horizontal line with very dissatisfied (score 0) and very satisfied (score 10) Secondary outcome measures: • In the ICF domain of body functions and structures, the original Ashworth scale was used • In the ICF domains of activities and participation, the Dutch versions of the PEDI and the Gross Motor Function Measure (GMFM) • Health related quality of life (HRQL) measured using the Dutch version of the Child Health Questionnaire-Parent Form 50 (CHQ-PF50). The CHQ-PF50 is a generic child health instrument designed to measure the physical and psychological well being of children aged 5 years and older. Consists of several domains that are scored 0 to 100. Higher scores reflect a better HRQL.
LE	I
Number of Patients and Characteristics	17 children: • 9 girl, 8 boys • Age between 7 and 16 years (mean age 13.2 years; SD 2.8) • 9 in the Intervention Group (CITB Group), 8 in the Control Group Inclusion criteria: • Age between 4 and 16 years • Spastic diplegia or tetraplegia as part of CP • In a mixed cerebral palsy syndrome, spasticity is the most prominent sign • Spasticity results in decrease in the quality of life of the child and / or its caregivers • Sufficient motivation for the study participation including availability for follow-up • Magnetic resonance imaging of the brain rules out progressive disease • Minimal weight of 20 kg (valid until January 1st 2004) • Child is able to understand and carry out instructions (valid until January 1st 2004) Exclusion criteria: • Hypersensitivity to baclofen • Contraindications for general anaesthesia • Insufficient general health • Intractable epileptic seizures • Infection of the lumbar skin • Systemic infection
Intervention	Continuous ITB infusion and standard treatment Programmable infusion pump (Medtronic, Inc., Minneapolis, MN)
Comparison	Standard treatment

Length of follow up (if applicable)	6 months
Outcome measures/ Effect size	Mean daily continuous ITB infusion dose:- • 67 µg (SD 25) right after pump implantation and 176 µg (SD 118) 6 months later Visual analogue scale (VAS) for individual problems per group: • Change from baseline to 6 months after treatment; Mean [Standard deviation (SD)] ° Improved with 4.0 (SD 1.7) in the CITB group and changed with – 0.2 (SD 1.3) in the control group, P = 0 .001. Visual analogue scale (VAS) for ease of care: • Change from baseline to 6 months after treatment; Mean [Standard deviation (SD)] ° Improved with 3.9 (SD 2.2) in the CITB group and changed with 0.1 (SD 1.6) in the control group, P = 0.008. Visual analogue scale (VAS) for pain: • Change from baseline to 6 months after treatment; Mean [Standard deviation (SD)] ° Improved with 4.2 (SD 2.9) in the CITB group and worsened with - 1.3 (SD 2.4) in the control group, P = 0.016. PEDI caregiver assistance scale of self-care domain: • Change from baseline to 6 months after treatment; Median (range) ° Did not significantly differ between both trial groups, 0.0 (-11.7 to 4.1) in the CITB Group and 0.0 (-16.0 to 16.0) in the Control group, P = 0.720 PEDI functional skills of self-care domain: • Change from baseline to 6 months after treatment; Median (range) ° Did not significantly differ between both trial groups, 0.0 (-7.4 to 5.7) in the CITB Group and 0.0 (-5.4 to -2.1) in the Control group, P=0.663 Ashworth score between both trial groups: • Significantly differed in favour of the CITB group for the right wrist flexors (P = 0.0380), left hip adductors (P = 0.025) and both hip flexors (right, P = 0.022, left, P = 0.043) ICF domains of activities and participation, GMFM-66: • Change from baseline to 6 months after treatment; Mean [Standard deviation (SD)] ° Improved with 1.2 points (SD 2.3) in the CITB group and worsened with - 1.6 points (SD 3.0) in the Control group, P = 0.028 The GMFM-88 sitting dimension: • Change from baseline to 6 months after treatment; Median (range) ◦ Improved with 3.3 points (0.0 to 10.0) in the CITB group and remained unchanged in the Control group; [median 0.0 points (-0.70 to 7.0), P = 0.085 The GMFM goal dimensions: • Change from baseline to 6 months after treatment; Median (range) ° Improved with 3.0 points (2.0 to 10.0) in the CITB group and with 1.3 points (-6.0 to 10.0) in the Control group, P = 0.140 CHQ-PF50 domains: • Change from baseline to 6 months after treatment; Mean [Standard deviation (SD)] ° Score for bodily pain and discomfort improved with 24.4 (SD 20.7) in the CITB group and worsened with – 10.6 points (SD 26.8) in the Control group, (P = 0 .014) ° Score for domains of mental health improved 9.1 points (SD 9.1) versus Control group – 3.5 points (SD 15.1), P = 0.045 ° Parental impact time improved by 5.2 points (SD 18.1) versus Control group – 19.8 points (SD 29.0), P = 0.043) ° Psychosocial summary score (CITB group) improved 3.4 points (SD 7.9) versus Control group – 5.7 points (SD 8.8), P = 0.027 **Authors conclusion** The authors concluded that CITB is effective in the treatment of carefully selected children with problems caused by intractable spastic CP.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	2. Hoving MA, van Raak E P.M, Spincemaille GHJJ, van Kranen-Mastenbroek VHJM, Kleef Mv, Gorter JW, Vles JSH. Safety and one-year efficacy of intrathecal baclofen therapy in children with intractable spastic cerebral palsy. European Journal of Paediatric Neurology. 2009;13:247-256.
Study Type / Methods	Prospective follow-up study of randomised controlled trial conducted at the University Hospital Maastricht in the Netherlands. The aim was to study the efficacy at 12 months and safety up to 24 months after the start of continuous intrathecal baclofen infusion (CITB) in children with intractable spastic cerebral palsy (CP). Nine girls and 8 boys, received Synchromed pump for continuous infusion of intrathecal baclofen. The effects and adverse events were prospectively recorded at regular follow-up visits (3 month) up to 24 months. Outcome measures included the 0-10 visual analogue scale (VAS) for individual problems, Gross Motor Function Measure (GMFM) and health related quality of life as measured with the Child Health questionnaire –PF50. Adverse events were recorded on standardised forms. Adverse event was defined as any undesirable experience occurring to a participant during the study. A serious adverse event was defined as nay untoward medical occurrence or effect that: (1) resulted in death; (2) was life threatening; (3) required hospitalisation or prolongation of existing hospitalisation; or (4) resulted in persistent or significant disability or incapacity. Non-parametric Wilcoxon Signed Rank Test was used to compare the results of the outcome measures at the 6-month and 12-month follow-up visit with those at baseline. Baseline measurements were carried out before pump implantation.
LE	II-2
Number of Patients and Characteristics	17 children, 9 girls and 8 boys participated in the Dutch ITB study: Aged 13.7 years (SD, 2.9; range 7 to 17) at the time of pump implantation
Intervention	Continuous ITB infusion and standard treatment. Synchromed pump
Comparison	No comparator
Length of follow up (if applicable)	24 months
Outcome measures/ Effect size	Mean daily continuous ITB infusion (CITB) dose:- • 61 µg (SD 27) directly after pump implantation,189 µg (SD 132) after 6 months and 233 µg (SD 170) after 12 months. Seven children took baclofen orally at the time of pump implantation. Six gradually discontinued the taking of oral baclofen during the first 10 postoperative days. In one child the dose was largely reduced. Visual analogue scale (VAS) for individual problems: • Change from baseline to 12 months after treatment; Mean [Standard deviation (SD)] ◦ Improved with 4.7 (SD 2.0), P = 0 .000. Visual analogue scale (VAS) for ease of care: • Change from baseline to 12 months after treatment; Mean [Standard deviation (SD)] ◦ Improved with 5.2 (SD 2.1), P = 0.000. Visual analogue scale (VAS) for pain: • Change from baseline to 12 months after treatment; Mean [Standard deviation (SD)] ◦ Improved with 5.4 (SD 2.7), P = 0.002. ICF domain of body functions and structures, change from baseline to 12 months after treatment: • H/M ratio of both legs decreased significantly (P < 0.001) Ashworth score: • Decreased significantly in 5 out of 8 upper-extremity muscle groups ($0.008 \leq p \leq 0.046$) and nine out of 14 lower extremity muscle groups ($0.002 \leq p \leq 0.046$) ICF domains of activities and participation, GMFM-66: • Change from baseline to 12 months after treatment; Mean [Standard deviation (SD)] ◦ Improved with 1.6 points (SD 3.1), P = 0.110 The GMFM- sitting dimension score: • Change from baseline to 12 months after treatment; Median (range) ◦ Improved with 3.3 points (- 4.0 to 22.0), P = 0.022 The GMFM goal dimension score: • Change from baseline to 12 months after treatment; Median (range) ◦ Improved with 4.0 points (0.0 to 26.0), P = 0.007 CHQ-PF50 domains: • Change from baseline to 12 months after treatment; Mean [Standard deviation (SD)] ◦ Score for bodily pain and discomfort improved with 25.6 points (SD 35.9), P = 0 .016 ◦ Score for domains of mental health improved with 9.8 points (SD 11.3), P = 0.007 ◦ Score for domains of psychosocial status improved with 5.5 points (SD 9.0), P = 0.088 PEDI Functional Skills and Caregiver Assistance scales did not improve with CITB Effects of common CP associated problems at 12 months: ◦ Speech improved in 3 out of 13 children, 9 no change, 1 became worse ◦ Swallowing improved in 2 out of 8 children, 5 no change, 1 became worse ◦ Sleep improved in 5 out of 7 children, 2 no change ◦ 4 out of 5 children could better operate their electric wheelchairs ◦ Transfers, all by carrying the child improved in all 4 children, 1 no change ◦ Constipation improved in 5 out of 14 children, 7 no change, and 2 became worse ◦ 6 children had epilepsy before CITB treatment, 2 improved, while 4 had no change Overall satisfaction: • 15 of the 17 children / or their parents stated that they would participate in all procedures again. **Authors conclusion** The authors concluded that CITB was effective at 12 months and safe up to 24 months for carefully selected children with intractable spastic CP. CITB relieved pain, facilitated ease of care and improved mental health. The majority of children could extend their activities and participation.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	3. Gilmartin R, Bruce D, Storrs BB, Abbot R, Krach L, Ward J, Bloom K, Brooks WH, Johnson DL, Madsen JR, McLaughlin JF, Nadell J. Intrathecal baclofen for management of spastic cerebral palsy: multicenter trial. Journal of Child Neurology. 2000;15:71-77.
Study Type / Methods	Phase 1, randomised, double blind placebo controlled trial (screening phase). Phase 2, open label (long-term infusion phase). Study was conducted in 12 centres, in the United States of America (U.S.A) initiated in 1992. The aim of this study was to assess the safety and efficacy of continuous intrathecal infusion of baclofen in patients with spastic cerebral palsy. Phase 1 involved a double-blind intrathecal bolus of 50 µg of Lioresal intrathecal (baclofen injection) or placebo (0.9% preservative-free sodium chloride injection), delivered by lumbar puncture, percutaneous spinal catheter, or implanted port with spinal. Oral baclofen was stopped prior to study participation unless discontinuation presented a hazard to the patient. The patients were assigned to a baclofen-placebo or a placebo-baclofen sequence with a 48-hour washout period between injections. The investigator, evaluator, patient, and caregiver were blinded to treatment regimen. All patient were monitored for safety and efficacy during the 3-day in patient period. The Ashworth Scale was used to quantify spasticity at baseline and 0.5, 1, 2, 4, 6, 8, and 24 hours after the bolus was delivered. The study blind was broken 12 to 24 hours after the second bolus. For those patients who received baclofen, a reduction of one point in the average Ashworth Scale score for all eight lower-extremity sites, maintained over two successive measurements between the 1 and 8 hour periods, identified them as candidates for pump implantation. Phase 2 consisted of an open-label, long-term, intrathecal infusion of baclofen. Clinical objective of phase 2 was to maintain an average Ashworth Scale score in lower extremities of 1 or 2, or to maintain optimal function. The study protocol required 10 routine visits in the first year following implantation. Spasticity was evaluated within 2 weeks of implantation, monthly for 6 months, and then at 3 month intervals. Pair-wise comparisons of average Ashworth Scale scores in lower extremities (primary endpoint) and upper extremities (secondary endpoint) at baseline and at 2,4,6, and 8 hours post injection were analysed using Wilcoxon Signed Rank Test.
LE	II-I
Number of Patients and Patient Characteristics	Phase 1 trial: 51 patients enrolled in the study: • 29 males , 22 females • Age; range (4 to 31.3 years), mean age (10.3 years), median age (11.2 years) • 4 had spastic paraplegia, 12 had spastic diplegia, 35 had spastic quadriplegia Phase 2 trial: • 44 patients received implants Inclusion criteria: • Age 3 years or older • Enough body mass to accommodate an implantable pump • Severe spasticity, Ashworth scale score of 3 or more in the lower extremity measurements
Intervention	Phase 1: Intrathecal bolus baclofen injection Phase 2: Intrathecal infusion of baclofen, SynchroMed Infusion system
Comparison	Phase 1: Placebo; 0.9% preservative free sodium chloride injection. Phase 2: No comparator
Length of follow up (if applicable)	Mean: 27.8 months, Range: 4.0 to 43.2 months

Outcome measures/ Effect size	Phase 1 (screening phase):- • Of the 51 patients who completed the intrathecal bolus screening, 7 withdrew: 3 had positive response to the placebo, 2 did not respond to a 50 µg bolus injection of baclofen and withdrew before getting higher bolus doses, 1 developed meningitis, and 1 had an adverse event of nausea, vomiting, elevated WBC, nystagmus and agitation. The investigator noted that this patient had intercurrent gastroenteritis. Efficacy of Baclofen Injection (Ashworth Scale Score): Clinically significant relief of spasticity, • Lower extremity Ashworth Scale Scores at 4 hours, Dose = 50 µg, Mean (SD), range: ◦ Baseline; 3.36 (0.61), 2.00 - 5.00 ◦ Placebo; 3.11 (0.69), 1.75 – 5.00 ◦ Baclofen; 2.14 (0.85), 1.00-4.75 P < 0 .001, placebo versus baclofen P < 0.001, baseline versus baclofen • Upper extremity Ashworth Scale Scores during screening with 50 µg bolus injection of baclofen, Mean (SD), range: ◦ Baseline; 2.21 (0.80), 1.00 - 4.5 ◦ 2 hours; 1.99 (0.81), 1.00 – 4.4 ◦ 4 hours; 1.92 (0.80), 1.00 – 4.4 ◦ 6 hours; 1.93 (0.79), 1.00 – 4.3 ◦ 8 hours; 1.96 (0.79), 1.00 – 4.3 P < 0.001, baclofen compared to baseline Phase 2 (chronic baclofen infusion):- • Of the 44 patients in phase 2, 7 withdrew after implantation: 2 developed an infection in the pump pocket, 2 because of family issues, 1 wanted to become pregnant, and 2 died (1 as a passenger in a motor vehicle accident and 1 of respiratory failure due to pneumonia). No patient withdrew from phase 2 because of lack of or loss of efficacy. Efficacy of Baclofen Injection (Ashworth Scale Score): • Average Lower- Extremity Ashworth Scale Scores, Average, range (SD): ◦ Baseline; 3.64, 2.0 - 5.0 (0.57) ◦ 6 months; 2.33, 1.0 - 3.8 (0.64) ◦ 12 months; 2.15, 1.1 - 3.3 (0.60) ◦ 24 months; 2.21, 1.1 - 3.5 (0.75) ◦ 39 months; 1.90, 1.3 - 2.8 (0.53) • Average Upper- Extremity Ashworth Scale Scores, Average, range (SD): ◦ Baseline; 2.54, 1.0 - 4.5 (0.98) ◦ 6 months; 1.80, 1.0 - 3.8 (0.72) ◦ 12 months; 1.73, 1.0 - 4.1 (0.66) ◦ 24 months; 1.72, 1.0 - 3.1 (0.69) ◦ 39 months; 1.34, 1.0 - 2.13 (0.50) Average Daily Dose of baclofen (µg/day): • Distribution of daily doses of baclofen Average, Median, range ◦ Implant; 78.0, 75.0, 50.0 - 120 ◦ 6 months; 206.6, 125.0, 32 – 490 ◦ 12 months; 265.2, 180.0, 25 –1350 ◦ 24 months; 293.0, 216.5, 25 - 1200 ◦ 39 months; 402.1, 275.0, 118-900 **Authors conclusion** The authors concluded that continuous intrathecal baclofen has been demonstrated as an effective method of reducing spasticity of cerebral origin. The treatment is relatively safe, minimally invasive, and reversible. This treatment system requires long-term monitoring by an experienced healthcare team. Long-term economic and qualitative effects on healthcare delivery to patients with spasticity remain to be evaluated.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	4. Krach LE, Kriel RL, Gilmartin RC, Swift DM, Storrs BB, Abbott R, Ward JD, Bloom KK, Brooks WH, Madsen JR, Mclaughlin JF, Nadell JM. GMFM 1 year after continuous intrathecal baclofen infusion. Pediatric Rehabilitation. 2005;8(3):207-213
Study Type / Methods	Prospective non controlled, open label, multi-centre study. Subjects in the study were in the follow-up phase of a previously reported prospective, double blind cross over study of a single dose of ITB versus placebo. Study was conducted in 12 centres, in the United States of America (U.S.A) initiated in 1992. The aim of this study was to determine whether there is an improvement in motor function following ITB as reflected by a change in Gross Motor Function Measure (GMFM) scores. The primary outcome measure was change in GMFM. GMFM is a standardised observational measure of gross motor function. A secondary outcome measure was subjective improvement as reported by subjects or their caretakers on a questionnaire. All subjects had completed a double blind study during which there was a favourable response to the bolus injection. All subjects included in data analysis had GMFM evaluations prior to and after 1 year of treatment with continuous infusion of intrathecal baclofen.
LE	II-2
Number of Patients and Patient Characteristics	44 of the 51 subjects in the original investigation received implantable pumps and were eligible to participate in the open label study. 13 of the 44 subjects subsequently were excluded: 4 had orthopaedic surgery, 2 had infections of the implanted drug delivery system, 1 became pregnant, 6 did not have 12 month GMFM data. 31 patients included in the study: • 19 males • 12 females • Age at implantation: range (4 to 29.5 years), mean age (11.9 years), median age (10.6 years) • 3 under 5 years old Inclusion criteria: • Age 3 years or older • Enough body mass to accommodate an implantable pump • Severe spasticity, Ashworth scale score of ≥ 3 in the lower extremity measurements • Favourable response to ITB bolus injection • Had GMFM evaluations prior to and after 1 year of treatment Definition: Functional classification of cerebral palsy (CP): Class 1= ambulatory without devices, Class 2 = ambulatory with orthoses or devices, Class 3 = mobility by crawling on hands and knees or independent wheelchair, Class 4 = non-ambulatory however having other purposeful motor activity.
Intervention	Intrathecal infusion of baclofen. SynchroMed Infusion System programmable pump (Medtronic)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Gross Motor Function Measure (GMFM) scores [Month 12 – baseline (Mean ± SD)]: GMFM dimensions (all subjects): • Improvement in all dimensions except walking and running ◦ Lying = 4.7 ± 8.9, P < 0.05 ◦ Sitting = 6.2 ± 9.9, P < 0.05 ◦ Crawling = 3.6 ± 8.0, P < 0.05 ◦ Standing = 6.5 ± 14.2, P < 0.05 ◦ Walking and running = 0.4 ± 3.2, P > 0.05 GMFM by age group and CP class: • Age category (years) ◦ < 8 = 4.1 ± 4.8, P < 0.05 ◦ 8-18 = 3.7 ± 5.2, P < 0.05 ◦ > 18 = 7.5 ± 8.0, P > 0.05 ◦ All subjects = 4.3 ± 5.4, P < 0.05 • CP Class ◦ 1 = 4.8 ◦ 2 = 6.2 ± 4.2, P < 0.05 ◦ 3 = 6.5 ± 8.5, P > 0.05 ◦ 4 = 3.0 ± 6.0, P > 0.05 ◦ 5 = 2.9 ± 2.4, P < 0.05 ◦ All subjects = 4.3 ± 5.4, P < 0.05 Ashworth scores: There was a statistically significant decrease (P < 0.05) in Ashworth scores for individuals with CP classes 2 to 5 Changes in GMFM versus changes in Ashworth scores: There was no significant correlation between the changes in GMFM and Ashworth scores (P = 0.543). However, there was a trend between improvement in lower extremity Ashworth scores and mean improvement in GMFM. For subjects with the greatest improvement in Ashworth scores (≥ 2.0 decrease) the corresponding mean improvement in GMFM was 6.94 ± 8.02. Subjective improvement as reported by subjects or their caretakers on a questionnaire: They reported improvement most often in motor control, positioning and endurance (60 to 70%). On the other hand, less than half observed improvement in speech, oral control, self cares, transfers or walking.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	5. Van Schaeybroeck P, Nuttin B, Lagae L, Schrijvers E, e Borghgraef C, Feys P. Intrathecal baclofen for intractable cerebral spasticity: A prospective placebo-controlled, double-blind study. Neurosurgery. 2000;46(3):603-612
Study Type / Methods	Randomised, double blind placebo controlled trial (screening phase). Open label (long-term infusion phase). Study was conducted at the University Hospital Gasthuisberg, Leuven, Belgium. The aim of this study was to;1) examine the effect of intrathecal baclofen (bolus injections and continuous infusion), 2) demonstrate functional improvement in severely disabled patients, 3) evaluate the effect on spasticity in different muscle groups **Screening** The screening trial was performed in a placebo-controlled fashion. A lumbar puncture was performed once daily, and injections of 25, 50, 75 or 100 µg of baclofen or saline were given in random order, starting with either 25 or 50 µg of baclofen or saline. The patient, family, and physical therapist were blinded to the bolus dose and the placebo injection. Spasticity was scored using the Ashworth scale and a visual analog score (VAS). A large range of muscle groups were evaluated using Ashworth scale by two experienced physical therapists. The "baseline spasticity score" was calculated as the mean spasticity score of all baseline evaluations during the screening period. After bolus injections with baclofen, evaluation was performed at 2, 4, and 6 hours. The VAS was calculated on the basis of a 10 cm line representing 0 to 100% severity of spasticity, on which the patients or their caregivers marked their perceived spasticity score. Implantation, follow-up, and dose reduction test. Eight patients underwent implantation of SynchroMed Infusion System programmable pump (Medtronic, Inc., Minneapolis, MN). The minimal effective bolus injection dose was doubled to calculate the starting chronic infusion dose. Outpatient follow-up was organised at 1,3,6,9, and 12 months, and thereafter according to the refilling requirements of the pump. During the first year of follow-up each patient was subjected to a blinded dose reduction test and (with the exception of one patient) to subsequent physiotherapeutic and subjective scoring.
LE	II-I
Number of Patients and Patient Characteristics	Screening phase: 11 patients enrolled in the study: • Patients with spasticity of cerebral origin (mainly cerebral palsy) • 5 females, 6 males • Patients were severe quadriparesis, as well as those with relatively good motor function Implantation, follow-up, and dose reduction test: • 8 patients (6 patients follow-up for 2 years) • 4 of the six patients who received implants were extremely disabled, wheelchair bound, and mentally retarded Inclusion criteria: • Severe quadriparesis • Relatively good motor function • Treatment with oral antispasmodic was either inefficient or provoked intolerable side effects Exclusion criteria: • Child bearing potential • Pregnancy • Renal or hepatic dysfunction
Intervention	Screening phase: Intrathecal bolus baclofen injection Implantation, follow-up, and dose reduction test: Intrathecal infusion of baclofen, SynchroMed Infusion System programmable pump (Medtronic)
Comparison	Screening phase: Placebo; Saline. Long term infusion phase: No comparator
Length of follow up (if applicable)	2 years
Outcome measures/ Effect size	Screening phase • Mean Ashworth scale scores:- ◦ In 8 of 11 patients, the effect of intrathecal bolus injections with baclofen was dose dependent, and it differed clearly from the placebo effect (placebo versus best result on the Ashworth scale after bolus injection, $P < 0.0001$ for six most reactive muscle (MRMs), $P < 0.0001$ for six most spastic muscle (MSMs), $P < 0.0001$ for all muscle (AMs). Continuous infusion • Mean Ashworth Scale scores:- ◦ Data on 6 patients. ◦ Spasticity scores at 12 months remained significantly below the baseline values; $P = 0.001$ for MRMs, $P = 0.0001$ for MSMs, $P = 0.002$ for AMs ◦ Effect in upper limbs was less prominent than in the lower limbs: ◦ Upper-extremity, significant effect of bolus injections on upper-extremity spasticity ($P = 0.00003$), the effect was no longer present during continuous infusion ($P = 0.156$) ◦ In the lower limb joints, the chronic effect was significant in the hips ($P = 0.001$) and in the knees ($P = 0.05$), but was not significant in the ankles ($P = 0.2$) • VAS for spasticity:- ◦ After bolus injection of baclofen, a clear reduction in the VAS ($P = 0.0078$) was observed, and this effect was maintained during continuous infusion ($P = 0.03$). • Effect on functional abilities, spasms, and pain: ◦ Pain diminished in all patients ◦ All patients reported a better quality of life ◦ Overall functional scores demonstrated no significant changes. Four of the six patients who received implants were extremely disabled, wheelchair bound, and mentally retarded. In these patients, only minor functional improvements could be achieved. An exception was one patient (Patient 1), who had dystonic postures. After treatment was initiated, this patient could drive her wheelchair autonomously and was able to draw. Furthermore, for severely disabled patients there was an improvement in hygiene, comfort, nursing, and physiotherapeutic possibilities. In all but one of the patients receiving implants, oral antispasmodic treatments were discontinued. • Dose reduction test during continuous infusion: ◦ After a blinded dose reduction, 5 patients reported a deteriorated functionality after dose reduction, four of whom exhibited a subjective increase of spasticity. There was confirmed Ashworth scale score in only two patients. **Authors conclusion** The authors concluded that intrathecal administration of baclofen is a safe and effective treatment for spasticity of cerebral origin. Functional improvement was demonstrated. The presence of a placebo effect on the spasticity scores suggests the need for double-blind screening in each patient.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	6. Meythaler JM, Guin-Renfroe S, Hadley MN. Continuously infused intrathecal baclofen for spastic/ dystonic hemiplegia: A preliminary Report. American Journal of Physical Medicine & Rehabilitation. 1999;78(3):247-254
Study Type / Methods	Randomised, double blind placebo controlled, cross over trial (screening phase). Open label (long-term infusion phase). Study was conducted at the tertiary care university medical centre (Alabama School of Medicine, Birmingham, Alabama). The aim of this study was to determine whether continuous intrathecal delivery of baclofen will control spastic hypertonia associated with long-standing hemiplegia from acquired brain injury. **Screening** Patients were randomised to receive either a bolus injection of intrathecally administered preservative- free normal saline or 50 µg of ITB. The crossover phase of the trial evaluation occurred during the 2nd outpatient clinic visit at least 48 hour after the initial administration. At the same time, the opposite substance was injected in the same manner as before, with subsequent data collection being the same as that which took place during the initial trial. Neither the patient nor the investigator knew which substance was injected until after the second trial phase was completed. Data on Ashworth scale score, and deep tendon reflexes score were then collected at 1,2,4 and 6 h post injection by the same investigator on the affected upper limb and lower limb side. Those who dropped an average of two points on their affected lower limb side Ashworth scores were then offered computer-controlled pump implantation for continuous intrathecal administration of baclofen. **Implantation** After implantation of the infusion device, patients were followed-up on an outpatient basis for refilling and dosage adjustment. Dose adjustments most basic goal being two-point decrease of the tone or spasm frequency scales in the affected limbs. The statistical study design is an A-B case control design, with each patient used their own control. Data are presented as means and standard deviation (SD). Rather than consider each muscle separately, average scores for muscle tone, spasms, and reflexes were averaged for the upper limb or lower limbs for each patient.
LE	II-I
Number of Patients and Patient Characteristics	6 patients enrolled in the study: • 4 women, 2 men • Average age = 50 ± 8.9 year (SD) • 3 patients had suffered a traumatic brain injury and 3 patients had suffered a unilateral stroke in the cerebrum • Average tone before treatment (range from 2.6 to 4.8) Criteria for inclusion in the study: • Between 14 and 75 year of age • Diagnosis of severe chronic spastic hypertonia in the lower limbs for at least 6 months duration that was defined by an average Ashworth score of at least three in the effected limbs or an average spasm score of at least two in the affected limb • Either failure to respond satisfactorily to treatment with oral antispasticity medications or the occurrence of unacceptable side effects at effective treatment dosages Patients presented with normal tone and motor strength on one side and with the spasticity / dystonia on the other
Intervention	**Screening :** Intrathecal bolus baclofen injection 50 µg **Implantation :** Intrathecal infusion of baclofen. Programmable pump
Comparison	**Screening:** Placebo; preservative free normal saline injection. **Long term infusion phase;** No comparator
Length of follow up (if applicable)	3 months
Outcome measures/ Effect size	Efficacy of continuous intrathecal infusion of baclofen (differences between baseline and after 3 months of treatment) Lower limbs (affected side): • Average lower limb Ashworth score [Mean (SD)] ◦ Decreased 1.8 points from 3.7 ± 1.0 points before treatment to 1.9 ± 0.6 points after 3 months, P < 0.0001 • Average lower limb reflex score [Mean (SD)] ◦ Decreased 1.3 points from 1.8 ± 1.3 points before treatment to 0.5 ± 0.8 points after 3 months, P = 0.0208 • Average lower limb spasm score [Mean (SD)] ◦ Decreased 0.5 points from 1.3 ± 1.2 points before treatment to 0.8 ± 1.3 points after 3 months, P = 0.5 Lower limbs (normal side): • Average lower limb reflex score [Mean (SD)] ◦ Decreased 1.4 points from 1.6 ± 1.3 points before treatment to 0.2 ± 0.4 points after 3 months, P = 0.0051 Upper limbs (affected side): • Average upper limb Ashworth score [Mean (SD)] ◦ Decreased 1.3 points from 3.4 ± 0.9 points before treatment to 2.1 ± 0.9 points after 3 months, P = 0.0002 • The biceps reflex score [Mean (SD)] ◦ Decreased 0.7 points from 2.3 ± 0.5 points before treatment to 1.7 ± 0.5 points after 3 months, P = 0.1088 • Average upper limb spasm score [Mean (SD)] ◦ Decreased 0.8 points from 0.8 ± 1.3 points before treatment to 0.0 points after 3 months, P = 0.1797 Upper limbs (normal side): • Average reflex score [Mean (SD)] ◦ Decreased 0.7 points from 2.0 ± 0 points before treatment to 1.3 ± 0.5 points after 3 months, P = 0.0679 • Average Daily Dose of baclofen (µg/day) at the end of 3 months: ◦ 205.3 µg ± 148 (range; 100 to 500 ug/day) Functional status • Two patients (Patients 3 and 6), improved rapidly with respect to their functional status, improving from wheelchair-dependent to wheelchair independence with ambulation using assistive devices within 2 weeks of pump implantation • Another patient (Patient 4) went from ambulation with assistive devices to independent ambulation without any devices and walks up to 2 miles per day
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	7. Meythaler JM, Guin-Renfroe S,Brunner RC, Hadley MN. Intrathecal baclofen for spastic hypertonia from stroke. Stroke. 2001;32:2099-2109
Study Type / Methods	Randomised, double blind placebo controlled, cross over trial (screening phase) Open label (long-term infusion phase) Study was conducted at the tertiary care university medical centre (Alabama School of Medicine, Birmingham, Alabama) The aim of this study was to determine whether continuous intrathecal delivery of baclofen can effectively decrease spastic hypertonia due to stroke **Screening** Patients were randomised before the bolus to either 50 µg baclofen or preservative free normal saline via a coin toss. All boluses were at least 72 hours apart. Those who dropped an average of 2 points in either their affected lower extremity side Ashworth or Penn spasm frequency scores were then offered computer-controlled pump implantation for continuous ITB and followed prospectively for up to 12 months. Patients who had a partial drop (< 2 points) in the mean Ashworth scores or Penn spasm frequency scores but did not meet criteria for pump placement were given the option of a 75-to 100-µg bolus trial, which was not blinded. If, after this trial, they qualified the pump placement was offered. Both the raters and the patients were blinded until after the second bolus. **Implantation** After implantation of the continuous infusion device, patients were followed on an outpatient basis for refilling and dosage adjustment. The 5-point Ashworth (rigidity) scale was used to assess muscle tone in both lower extremities. A 4-point scale which reflected the number of spontaneous sustained flexor and extensor muscle spasms per hour was used. A 5-point scale documenting deep tendon reflexes was used at the biceps, patella and Achilles. The statistical study design is an A-B single case control design with each patient used as his or her own control. Data are presented as averages with standard deviations. Rather than consider each muscle separately, average scores for muscle tone, spasms, and reflexes were averaged for the upper extremities or lower extremities for each patient.
LE	II-I
Number of Patients and Patient Characteristics	Screening • 21 subjects. Average age = 53 years, range (16 to 86 years of age) • Criteria for inclusion in the study: ◦ > 16 years of age ◦ Diagnosis of severe chronic spastic hypertonia in the lower limbs for at least 6 months duration that was defined by an average Ashworth score of at least 2 in the affected extremities at the day of the first screening ◦ Failure to respond satisfactorily to treatment with maximum recommended doses of oral antispasticity medications or the occurrence of unacceptable side effects at effective treatment dosages Continuous Infusion of ITB • 17 adult CVA patients ◦ Average age = 50 years, range (16 to 86 years) ◦ All patients were > 6 months from the onset of stroke (mean 41 months, range 10 to 107 months) ◦ 4 followed up for 6 months, 13 were followed up for 1 year ◦ 11 were right CVA patients with left hemiparesis, 4 were left CVA with right-sided hemiparesis, 2 were brain stem stroke patients with quadriparesis
Intervention	Screening: Intrathecal bolus baclofen injection 50 µg Implantation: Intrathecal infusion of baclofen. Programmable pump
Comparison	Screening: Placebo; preservative free normal saline injection. Long term infusion phase; No comparator
Length of follow up (if applicable)	1 year

Outcome measures/ Effect size	Bolus trial Two patients in the study who failed a bolus of 50 µg ITB did not respond to a larger dose of 100 µg. Lower extremities: • Significant differences noted in the average lower extremity Ashworth score, spasm score and reflex score between the active drug and placebo at 4 hours and 6 hours ($P < 0.0001$, $P = 0.0077$, and $P < 0.0001$, respectively) Upper extremities: • Statistically and clinically significant meaningful differences between the active drug and placebo at 6 hours after administration for upper extremity muscle tone ($P < 0.001$), spasm frequency ($P = 0.0117$), and reflex scores ($P = 0.0006$) Continuous Infusion of ITB for up to 1 year 19 patients were implanted. Two implanted patients (subjects 18 and 19) were dropped from the data analysis: • One developed Chronic hepatitis C • One was a paediatric patient Lower extremities (affected side): • Average lower extremity Ashworth score [Average (SD)] ◦ Decreased 1.9 points from 3.7 ± 1.0 points before treatment to 1.8 ± 1.1 points after treatment, $P < 0.0001$ • Average lower extremity spasm score [Average (SD)] ◦ Decreased 0.6 points from 1.2 ± 1.3 points before treatment to 0.6 ± 1.0 points after treatment, $P = 0.4282$ • Average lower extremity reflex score [Average (SD)] ◦ Decreased 1.4 points from 2.4 ± 1.3 points before treatment to 1.0 ± 1.3 points after treatment, $P < 0.0001$ Upper extremities (affected side): • Average upper extremity Ashworth score [Average (SD)] ◦ Decreased 1.4 points from 3.2 ± 1.1 points before treatment to 1.8 ± 0.9 points after treatment, $P < 0.0001$ • Average upper extremity spasm score [Average (SD)] ◦ Decreased 0.4 points from 0.7 ± 1.0 points before treatment to 0.3 ± 0.8 points after treatment, $P = 0.8685$ • The biceps reflex score [Average (SD)] ◦ Decreased 1.1 points from 2.4 ± 0.8 points before treatment to 1.5 ± 1.2 points after treatment, $P = 0.3337$ ITB Effects on Normal Extremities • Average lower extremity reflex score [Average (SD)] ◦ Decreased 1.6 points from 1.9 ± 0.8 points before treatment to 0.3 ± 0.7 points after several months to 1 year, $P < 0.0001$ • Average upper extremity reflex score [Average (SD)] ◦ Decreased 1.2 points from 1.9 ± 0.7 points before treatment to 0.7 ± 0.9 points after treatment, $P = 0.0858$ • No noted motor weakness on the normal side throughout the study utilising the standard 1 to 5 motor strength testing for the same joints as utilised for the Ashworth score. • Dosage of baclofen: ◦ Average dosage of ITB to achieve this reduction was 268 ± 175 ug/day (range; 500 to 660 ug/day) • Functional status ◦ Three patients went from wheelchair dependence to independent ambulation with assistive devices ◦ All dependent patients were more comfortable and were easier to manage at home with regard to hygiene, activities of daily living (ADL), and assisted transfers **Conclusion** The authors concluded that intrathecal infusion of baclofen is capable of maintaining a reduction in the spastic hypertonia resulting from stroke.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	8. Middel B, Kuipers-Upmeijer H, Bouma J, Staal M, Onema D, Postma T, Terpstra S, Stewart R. Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. J Neurol Neurosurg Psychiatry. 1997;63:2014-209
Study Type / Methods	Double blind, randomised, controlled trial, followed by observational longitudinal study at nine Dutch Hospitals. The aim of the study was to compare clinical effectiveness and health related quality of life in patients with severe spasticity who received intrathecal baclofen or a placebo. During the first 13 weeks after implantation of a SynchroMed programmable pump, the patients were randomly assigned to either baclofen (n=12) or a placebo (n=10). Both patient and doctor were blinded during the first 13 weeks after implantation. A maximum of 2 increases was made during the placebo controlled phase. Baclofen, placebo, and oral medication were supplied by the hospital pharmacist in a standard set of blank packages. The placebo controlled phase was followed by a 52 week observational longitudinal follow up phase. The questionnaires were administered at the start of the study, at 4 and 13 weeks after the start of the placebo controlled phase, and at 26 and 52 weeks of the follow up phase. Clinical efficacy was assessed by Ashworth scale, spasm score and self reported pain and health related quality of life by sickness impact profile (SIP) and the Hopkins symptom checklist (HSCL). The modified Ashworth scale has 4 grades: grade 0 (no increase in tone), grade 1 (slight increase in tone, but the affected part is moved in flexion or extension), grade 2 (more pronounced increase in tone, but affected part easily flexed), grade 3 (considerable increase in tone; passive movement difficult), grade 4 (affected part rigid in flexion or extension). The spasm score evaluates the frequency of spasms with score: 0 (no spasm), 1 (mild spasms induced by stimulation), 2 (infrequent spasms occurring less than once per hour), 3 (spasms occurring more than once per hour) and 4 (spasms occurring more than 10 times per hour). Pain was measured on a 10 point self assessment scale with a sum score ranging from 0 to 10, where 0 = having no pain and 10 = having unbearable pain. The sickness impact profile (SIP) is a behaviour based self reported measure that is used to quantify sickness related dysfunction. Patients are asked to complete a standardised questionnaire consisting of 136 items aggregated into 12 domains of daily functioning. The Hopkins symptom check list (HSCL) was translated and validated in Dutch. It consists of 57 items with two subscales (physical health and mental health) and an overall scale. According to Cohen, an effect size of 0.20 implies a small effect, 0.50 a medium effect, and ≥ 0.80 a large effect
LE	II-I
Number of Patients and Patient Characteristics	22 patients: • 10 males (45%), 12 females (55%) • Mean age (SD) = 48.3 (12.7) years, range (19-70 years) • 59% had multiple sclerosis, 41% had spinal cord injury Inclusion criteria: • Aged 18 years or over with chronic disabling spasticity of spinal origin inhibiting personal care, sitting, lying, and transfers, accompanied by pain and stiffness, or disturbed sleeping • Insufficient response to treatment with maximum doses of oral baclofen, dantrolene, and tizanidine • Sufficient understanding of the consequences of the treatment Exclusion criteria: • Pregnant • No neurological symptoms of supraspinal origin • Allergic to baclofen
Intervention	Continuous ITB infusion / Continuous ITB infusion, SynchroMed programmable pump
Comparison	First 13 weeks; placebo. 52 weeks; No comparator
Length of follow up (if applicable)	13 weeks / 52 weeks

Outcome measures/ Effect size	3 month outcome of baclofen and placebo for severe spasticity a. Differences between the groups (baclofen versus placebo) after 3 months: • Spasm score, Mean (SD): ◦ Differed slightly ◦ Baclofen, 1.65 (1.11) versus Placebo, 1.81 (0.76), P < 0.05, effect size = 0.20 • Ashworth scale, Mean (SD): ◦ Large difference ◦ Baclofen, 1.51 (1.20) versus Placebo, 2.87 (0.57), P < 0.01, effect size = 1.40 • Self reported pain score, Mean (SD): ◦ Large difference ◦ Baclofen, 2.75 (3.22) versus Placebo, 5.94 (3.57), P < 0.01, effect size = 0.94 • Health related quality of life: ◦ SIP and HSCL showed no significant differences b. Differences within the baclofen and placebo group (3 months versus baseline): • No significant changes for any of the outcomes in the placebo group after 3 months • Baclofen group showed significant changes in the following outcome measures: • Spasm score, Mean (SD): ◦ 3 months, 1.65 (1.11) versus baseline, 2.23 (0.54), P < 0.05, effect size = 0.74 • Ashworth scale, Mean (SD): ◦ 3 months, 1.51 (1.20) versus baseline, 2.51 (0.70), P < 0.05, effect size = 1.12 • Self reported pain score, Mean (SD): ◦ Large difference ◦ 3 months, 2.75 (3.22) versus baseline, 4.30 (2.98), P (NS), effect size = 0.72 • Overall SIP score, Mean (SD): ◦ 3 months, 27.79 (5.32) versus baseline, 31.72 (9.80), P < 0.05, effect size = 1.00 • SIP sleep and rest score, Mean (SD): ◦ 3 months, 16.2 (10.35) versus baseline, 12.33 (12.27), P < 0.05, effect size = 0.71 • SIP mobility score, Mean (SD): ◦ 3 months, 16.69 (12.29) versus baseline, 31.99 (17.40), P < 0.01, effect size = 1.35 • SIP physical dimension score, Mean (SD): ◦ 3 months, 35.10 (5.41) versus baseline, 39.98 (9.78), P < 0.05, effect size = 1.07 • SIP psychosocial score, Mean (SD): ◦ 3 months, 12.26 (9.87) versus baseline, 16.03 (13.69), P < 0.05, effect size = 0.74 • HSCL overall score, Mean (SD): ◦ 3 months, 20.67 (11.78) versus baseline, 30.0 (12.54), P < 0.001, effect size = 1.34 • HSCL mental health score, Mean (SD): ◦ 3 months, 5.00 (4.28) versus baseline, 7.83 (4.97), P < 0.01, effect size = 1.28 • HSCL physical health score, Mean (SD): ◦ 3 months, 4.00 (3.44) versus baseline, 4.17 (3.16), P (NS) Clinical outcome measures, SIP and HSCL one year after baclofen infusion versus baseline: • Spasm score, Mean (SD): ◦ 1 year, 0.62 (0.75) versus baseline, 2.16 (0.48), P = 0.003, effect size = 3.05 • Ashworth scale, Mean (SD): ◦ 1 year, 0.44 (0.51) versus baseline, 2.87 (0.54), P = 0.002, effect size = 6.23 • Self reported pain score, Mean (SD): ◦ 1 year, 1.97 (2.95) versus baseline, 4.57 (3.23), P = 0.009, effect size = 1.07 • Overall SIP score, Mean (SD): ◦ 1 year, 25.13 (9.61) versus baseline, 31.28 (7.93), P = 0.005, effect size = 0.99 • SIP sleep and rest score, Mean (SD): ◦ 1 year, 13.99 (10.53) versus baseline, 20.48 (12.48), P = 0.01, effect size = 0.95 • SIP mobility score, Mean (SD): ◦ 1 year, 25.16 (19.50) versus baseline, 35.10 (19.64), P = 0.02, effect size = 0.73 • SIP physical dimension score, Mean (SD): ◦ 1 year, 33.44 (12.73) versus baseline, 41.48 (8.07), P = 0.03, effect size = 0.86 • SIP recreation and pastimes score, Mean (SD): ◦ 1 year, 30.53 (22.35) versus baseline, 42.47 (22.47), P = 0.04, effect size = 0.63 • SIP body care and movement score, Mean (SD): ◦ 1 year, 41.44 (18.72) versus baseline, 50.62 (19.30), P = 0.02, effect size = 0.64 • SIP psychosocial score, Mean (SD): ◦ 1 year, 10.96 (10.18) versus baseline, 14.80 (11.72), P = Not significant • HSCL total score, Mean (SD): ◦ 1 year, 22.11 (12.09) versus baseline, 29.00 (12.71), P = 0.01, effect size = 0.87 • HSCL physical health score, Mean (SD): ◦ 1 year, 3.66 (3.03) versus baseline, 4.89 (2.87), P = 0.01, effect size = 0.86 • HSCL mental health score, Mean (SD): ◦ 1 year, 5.44 (4.57) versus baseline, 7.17 (5.56), P = Not significant **Authors conclusion** The authors concluded that intrathecal baclofen delivered by an implanted, programmable pump resulted in improved self reported quality of life as assessed by the SIP, and HSCL physical health dimensions also suggest improvement.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	9. Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. J Neurosurg. 1996;85:452-457
Study Type / Methods	Pre and post intervention study conducted at Boston University Medical Centre. The aim of the study was to determine the efficacy, safety, and cost-effectiveness of intrathecal baclofen delivered by a programmable pump for the chronic treatment of severe spasticity. 69 patients with severe spasticity of spinal cord origin that was refractory to oral baclofen or who experienced intolerable side effects with this form of the drug were screened. The first nine participated in a double-blinded, randomised, placebo (normal saline) controlled trial to determine response to a bolus dose of ITB. Subsequent patients were enrolled in an open-labelled treatment protocol without a placebo trial. All passed the screening and the pump was implanted in 59 patients. Spasticity scores and medical costs before and after surgery were analysed.
LE	II-2
Number of Patients and Patient Characteristics	66 patients with intractable spasticity of spinal origin. • Of these, 59 underwent implantation. • 27 had SCI, 26 has MS, 2 had familial spastic paraparesis, 4 others • 35 males, 24 females • Mean age = 42 years (ranged, 16 to 73 years) Severe spasticity defined as Ashworth score of 3 or higher or spasm score of 2 or higher.
Intervention	Continuous ITB infusion and standard treatment A programmable pump (SynchroMed Infusion System; Medtronic)
Comparison	No comparator
Length of follow up (if applicable)	Mean; 42 months (range, 23 to 70 months)
Outcome measures/ Effect size	Mean daily continuous ITB infusion dose:- • The dose increased from an average of 126 µg daily (range 14-280 µg) initially, to 256 µg at 6 months, and 272 µg at 12 months. The daily dose remained stable at an average of 276 µg at 24 months and 275 µg at 48 months, with a range of 42 to 700 µg. Difference between mean values preoperatively and at last follow-up, Mean P value: • Ashworth Scale Score; 4.3 preoperatively decreased to 1.4, $P < 0.0005$ • Spasm score; 3.6 preoperatively decreased to 0.5, $P < 0.0005$ **Activities of daily living:** Several patients found that activities of daily living such as transferring from wheel chair to bed were easier to accomplish. Muscle aches and pain, sleeplessness, and overall misery associated with uncontrolled spasm were considerably improved. One college student's grades sharply improved because he was more alert after discontinuing large doses of oral antispasmodic medications. Several females found that maintaining personal hygiene was more satisfactory when they no longer had adductor spasticity and scissoring at the hips. Four reported that they were able to have sexual intercourse. Some male patients also found sexual intercourse easier. For ambulatory patients were able to walk with less effort, whereas one patient who had previously been wheelchair bound became ambulatory. Voice was clearer in four patients,a finding confirmed by family members. The mechanism involved appears to be relief of intercostals and oropharyngeal spasms. A number of patients who had previously felt embarrassed by their severe spasms in public were able to resume their social lives. Two previously unemployed patients became gainfully employed, one as a taxi driver. With fewer spasms eliminated, a number of patients took fewer sick days off from work. **Hospitalisation:** Reduction in the average length of hospitalisations, but no change in the overall utilisation of outpatient resources during the first year after the pump was implanted. For the year prior to the implantation, excluding days spent on screening, the 10 patients had 12 hospitalisations with an average length of stay of 7.9 days, for a total of 95 days. For the first year post implantation, excluding the implant itself, they had 12 hospitalisations, with an average length of stay of 5.7 days, for a total of 68 days. The net reduction in hospital days was 27, for an average reduction of 2.7 hospital days per patient. **Authors conclusion** The authors concluded that intrathecal baclofen delivered by an implanted programmable pump is safe, effective, and cost-effective method for treatment of severe intractable spinal spasticity.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	10. Gray N, Morton RE, Brimlow K, Keetley R, Vloeberghs M. Goals and outcomes for non ambulant children receiving continuous infusion of intrathecal baclofen. European Journal of Paediatric Neurology. 2012;16:443-448
Study Type / Methods	Pre and post intervention study conducted at the National Nottingham ITB service, United Kingdom. The aim of the study was to evaluate the success of goals and compare these to actual outcomes in severely disabled children receiving continuous ITB. The participants were also part of a controlled prospective study of ITB in children, which also investigated function, participation in society and quality of life. Children attending the national Nottingham Children ITB service were recruited from 2003 to 2007 who met the following inclusion criteria: • They were to be fitted with an UTB pump on the basis of severe spasticity that reduced function, caused pain or interfered with the ease of care • Had a diagnosis of cerebral palsy, were non ambulant; GMFCS groups IV-V, aged 5 to 15 years • Able to be assessed at three specific times, before pump fitment, then 9 and 18 months after Prior to pump insertion, 3 specific goals were set between the caregiver, physiotherapist and if possible the child. Goals included function, ease of care, mood, or prevention of deformity. The goals were set as a simple statement implying overall benefit in all aspects. These were reviewed at the assessments, together with caregivers' views of the outcome of treatment in 14 different aspects. At the first and the last assessment, the degree of deformity of the hips and spine were reviewed, and orthopaedic surgeons were asked to predict what surgery would be needed in the next 2 years.
LE	II-2
Number of Patients and Patient Characteristics	37 children: • 19 males, 18 females • Mean age (SD) = 10.16 (3.25) years. Median age (range) = 10.0 (3 to 15) GMFCS level: 18 level IV, 19 level V CP type: 13 diplegia, 24 quadriplegia Dyskinesia present: 6
Intervention	Continuous ITB infusion. Continuous infusion pump, Medtronic
Comparison	No comparator
Length of follow up (if applicable)	18 months
Outcome measures/ Effect size	Mean and range of intrathecal baclofen dose at each assessment period: • At 9 months, 200 µg (50 to 650 µg baclofen) • At 18 months, 250 µg (35 to 1000 µg baclofen) Modified Ashworth Scale, Mean (SD), P value compared to baseline: ◦ At baseline, 2.43 (0.81) ◦ At 9 months, 1.36 (0.75), $P < 0.05$ ◦ At 18 months, 0.91 (0.51), $P < 0.05$ Achievement of goals at 9 and 18 months: ◦ All three set goals were attained by 80% of children at 9 and 18 months ◦ The most common successful outcomes were ease of nursing care, better sitting, spasm reduction, more relaxed / better mood, and improved sleep Changes in the 14 standardised treatment outcomes at 9 months and 18 months: ◦ Overall, there was an average achievement of 6.8 of the 14 outcomes at 9 months, and 7.0 at 18 months ◦ The score given by the caregivers for overall treatment was 7.6 at 9 months and 8.2 at 18 months, range 2 to 10. • Deformities of the hip and spine continued to occur • The predicted number of orthopaedic operations before and after ITB remained unchanged **Authors conclusion** The authors concluded that ITB is a major treatment for children with severe disability and should be undertaken with understanding of what can and cannot be achieved, before allowing realistic goals to be set.
General comments	Industry sponsored

Evidence Table : Effectiveness
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	11. Natale M, Mirone G, Moraci RA. Intrathecal baclofen therapy for severe spasticity: Analysis on a series of 112 consecutive patients and future prospectives. Clinical Neurology and Neurosurgery. 2012;114:321-325
Study Type / Methods	Pre and post intervention study conducted at the Second University of Naples SUN, Naples, Italy. The aim of the study was to discuss new indications and screening tools, appropriate surgical timing and compliance avoidance. Between 2/9/2000 and 31/12/2007, a total of 65 consecutive patients all with severe, progressive and refractory to medical therapy spasticity from different causes were evaluated for chronic intrathecal baclofen infusion after signature of informed consent. The other 47 patients were referred to the neurosurgery department after the implantation in two secondary centres for refilling of the pumps, daily dose titration and clinical follow-up. The neurological conditions were evaluated by the Modified Ashworth Scale (MAS) for the rigidity which was performed by two experienced physical therapists. The MAS scale was assessed for every patient before and after test and at follow-up time. The Penn Spasm frequency scale (SFS) was used for evaluating the spasms frequency in both the lower and the upper extremities. Pain was measured on a 10 point self assessment Visual Analogical Scale (VAS) with a score ranging from 0 to 10, where 0 means no pain and 10 means having unbearable pain. Ambulatory patients underwent preoperative instrumented gait analysis prior to and 4 hour following the screening test. The bolus screening (ranging from 25 µg to 100 µg was administered by a lumbar puncture at L3 ± L4 interspaces. Response was considered positive if there was an improvement of two or more points in the Ashworth scale for at least 4-6 h after the test. In case of positive response, a continuous infusion pump (Synchromed or Synchromed II, Medtronic Inc., Minneapolis, MN USA) was implanted.
LE	II-2
Number of Patients and Patient Characteristics	112 patients: • 63 males (56%) 49 females (44%). • Average age = 43.2 years (range; 7-63 years) • 74 (66%) had quadriparesis, 34 (30.4%) had a paraparesis, 4 (3.6%) were hemiplegic, 77 (68.7%) were non ambulatory, while 35 (31.3%) were ambulatory Causes of spasticity: • Multiple sclerosis (25 cases) • Cerebral palsy (21 cases) • Traumatic brain injury (10 cases) • Anoxic acquired brain injury (12 cases) • Spinal cord injury (15 cases) • Familial paraparesis (7 cases) • Friederich's ataxia (4 cases) • Adrenal leukodistrophy (3 cases) • Amyotrophic lateral sclerosis (4 cases) • Transverse myelitis (8 cases) • Syringomyelia (2 cases) • Rigid spine syndrome (1 case) Inclusion criteria: • Chronic severe disabling spasticity (score > 3 in the MAS) inhibiting or influencing personal care, sitting, lying, and transfers, accompanied by pain and stiffness, or disturbed sleeping • Failure of oral antispastic drugs • Absence of block in cerebrospinal circulation • No allergy to medication or pregnancy • Positive response to bolus intrathecal administration
Intervention	Continuous ITB infusion All patients started with simple continuous infusion after surgery. Complex infusion was selected in 56 patients (5)%), from 3 to 27 months (mean 14 months) after surgery. Medications used: Baclofen, 2000 µg/ml (95 patients), Baclofen, 500 µg/ml (15 patients), Morphine 10 mg/h with baclofen 1000 µg/ml (1 patient) Continuous infusion pump (Synchromed or Synchromed II, Medtronic Inc., Minneapolis, MN USA)
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up time; 55 months (range: 12 to 72 months)
Outcome measures/ Effect size	Daily baclofen dose varied between 23 µg and 500 µg with a mean of 150 µg/day. After screening test: • Modified Ashworth Scale (MAS), Mean ± SD: ◦ Decreased from 4.5 ± 0.6 points to 2.2 ± 0.4 points in the lower limbs and from 3.2 ± 0.4 points to 1.8 ± 0.3 points in the upper limbs. • Penn Spasm Frequency Scale , Mean ± SD: ◦ Decreased from 2.9 ± 0.4 to 1.2 ± 0.2. Last follow-up after baclofen infusion versus baseline: • Modified Ashworth Scale (MAS), Mean ± SD: ◦ Decreased from 4.5 ± 0.5 points preoperatively to 1.2 ± 0.4 points on chronic intrathecal baclofen. • Penn Spasm Frequency Scale , Mean ± SD: ◦ Decreased from 3.2 ± 0.4 preoperatively to 0.8 ± 0.2 on chronic intrathecal baclofen.
General comments	Pain score result not reported.

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	12. UCAR T, Kazan S, Turgut U, Karaman Samanci N. Outcomes of Intrathecal Baclofen (ITB) therapy in spasticity. Turkish Neurosurgery. 2011;21(1):59-65
Study Type / Methods	Pre and post intervention study conducted at Akdeniz University, Antalya / Turkey. The aim of the study was to evaluate the long-term efficacy of intrathecal baclofen on the spasticity and pain, and to evaluate the side effects of intrathecal baclofen. The medical records of 30 patients who underwent baclofen pump placement from 2000 to 2010 under the Department of Neurosurgery and followed up at the Department of Physical Medicine and Rehabilitation at Akdeniz University, Antalya / Turkey were reviewed. After signing an informal consent form for ITPB therapy, patients underwent a screening procedure to determine responsiveness to ITB. All subjects were given a test bolus 50 µg baclofen by lumbar puncture. The response was considered positive is there was an improvement of two or more points on Ashworth scores. In case of positive response, a continuous infusion pump was implanted. All patients were evaluated before the treatment, during the intrathecal bolus test with ITB, and follow-up period (two months after the pump implantation, then every 3 months). Patients' evaluation was done using spasticity measures (Ashworth scale). Activities of daily living were measured using the Barthel Index preoperatively and the following year. Handicap was measured by the Rankin Scale. Pain was assessed with a self-reported visual analogue scale from 0 to 10.
LE	II-2
Number of Patients and Patient Characteristics	30 patients: • 19 males, 11 females • Mean age = 30.10 ± 16.09 years • All study subjects had diffuse chronic, severe, and generalised spasticity of at least 3 months duration (Ashworth score ≥ 3), and had failed to respond adequately or had experienced untoward side effects from various oral antispastic drugs included baclofen • Aetiology of spasticity: ◦ 18 supraspinal spasticity (Cerebral palsy / brain injury), 12 had (Spinal Cord Injury)
Intervention	Continuous ITB infusion All patients started with simple continuous infusion after surgery. Complex infusion was selected in 56 patients (5%), from 3 to 27 months (mean 14 months) after surgery. Medications used: Baclofen, 2000 µg/ml (95 patients), Baclofen, 500 µg/ml (15 patients), Morphine 10 mg/h with baclofen 1000 µg/ml (1 patient) Synchromed infusion pump (Medtronic, Inc., Minneapolis, MN, USA).
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up period; 27.60 ± 14.66 months (range: 1 to 62 months). 5 patients treated for more than 48 months, 8 more than 36 months
Outcome measures/ Effect size	First year follow-up after baclofen infusion versus before treatment: • Ashworth Score of the upper extremity, Mean ± SD: ◦ Decreased from 2.22 ± 1.82 before treatment to 1.07 ± 1.01, P < 0.005 • Ashworth Score of the lower extremity, Mean ± SD: ◦ Decreased from 3.81 ± 1.82 before treatment to 1.69 ± 1.08, P < 0.005 • Spasm Frequency score of the upper extremity, Mean ± SD: ◦ Decreased from 1.74 ± 1.81 before treatment to 0.82 ± 0.90, P < 0.005 • Spasm Frequency score of the lower extremity, Mean ± SD: ◦ Decreased from 2.96 ± 1.78 before treatment to 0.88 ± 0.97, P < 0.001 • Barthel Index, Mean ± SD: ◦ Increased from 38.70 ± 7.15 before treatment to 51.62 ± 14.69, P < 0.005 ◦ The most dramatic improvements of motor function were observed within the first year. Moreover, facilitation of transfer, active and passive physical therapy and nursing care were observed in all patients. • Pain (VAS), Mean ± SD: ◦ Decreased from 4.81 ± 4.17 before treatment to 1.00 ± 1.44, P < 0.005 • Rankin scale, Mean ± SD: ◦ Decreased from 5.91 ± 0.30 before treatment to 5.10 ± 0.56, P < 0.005 **Dosage:** The mean initial dose of ITB was 140 µg / day (range 90 µg to 340 µg). During the first year after the pump implantation, the dosage was progressively increased almost in all patients. Drug dosage remained stable after the first year, except for 4 patients where dosage adjustments was required. **Authors conclusion** The authors concluded that ITB therapy increases the quality of lifestyle and functional independence by reducing not only cerebral but also spinal related spasticity in appropriately selected cases.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	13. Ramstad K, Jahnsen R, Lofterod B, Skjeldal OH. Continuous intrathecal baclofen therapy in children with cerebral palsy-when does improvement emerge? Acta Paediatrica. 2010;99:1661-1665
Study Type / Methods	Pre and post intervention study conducted at Rikshospitalet, Oslo, Norway. The aim of the study was to explore the timing of effects of intrathecal baclofen therapy in children with cerebral palsy. All children with cerebral palsy (CP) who started continuous intrathecal use of baclofen (CITB) at Rikshospitalet, Oslo were enrolled. Inclusion lasted from September 2002 to September 2005. All patients underwent a successful test treatment with intrathecal baclofen before they receive a programmable Synchromed infusion pump (Medtronic, Inc., Minneapolis, MN, USA). Assessment were performed at the day before the pump implantation (T0) and at 6 (T1) and 18 months (T2) of CITB treatment. Parents were asked about their child's sleep and pain (frequency of awakenings during night on average the last 4 weeks, frequency of pain episodes when not sleeping on average the last 4 weeks and severity of pain on a 0-4 scale), and they were interviewed according to the Paediatric Evaluation of Disability Inventory (PEDI) Functioning Skills Scale and Caregiver Assistance Scale. Spasticity was rated on the Modified Ashworth Scale (MAS). Child's gross motor function was assessed according to Gross Motor Function Measure (GMFM-66). Experienced physiotherapists conducted the assessments.
LE	II-2
Number of Patients and Patient Characteristics	38 patients: • Median age at implantation was 103 months (range 30 to 186 months). • One patient discontinued CITB after 3 months because the family suspected intolerable side-effects (agitation). In two patients the pump had to be removed because of infection and the families did not want another pump. • The other 35 patients (25 boys and 10 girls) continued treatment until the third assessment at 18 months of treatment.
Intervention	Continuous ITB infusion. Programmable Synchromed infusion pump (Medtronic, Inc., Minneapolis, MN, USA).
Comparison	No comparator
Length of follow up (if applicable)	18 months
Outcome measures/ Effect size	Sleep disturbances and pain in 35 patients with CP during different stages of CITB treatment: • Number of awakenings during night, Median (range): ◦ Baseline (T0); 1.0 (0 to 25) ◦ 6 months (T1); 0.0 (0 to 10) ◦ 18 months (T2); 0.0 (0 to 10) ◦ Change (T0 - T1), P = 0.005 ◦ Change (T0 - T2), P = 0.006 ◦ Change (T1-T2), P = 0.731 • Pain frequency, Median (range): ◦ Baseline (T0); 2.0 (0 to 3) ◦ 6 months (T1); 1.0 (0 to 3) ◦ 18 months (T2); 1.0 (0 to 3) ◦ Change (T0 - T1), P = 0.000 ◦ Change (T0 - T2), P = 0.005 ◦ Change (T1-T2), P = 0.019 • Pain severity, Median (range): ◦ Baseline (T0); 2.0 (0 to 3) ◦ 6 months (T1); 1.0 (0 to 3) ◦ 18 months (T2); 1.0 (0 to 3) ◦ Change (T0 - T1), P = 0.005 ◦ Change (T0 - T2), P = 0.011 ◦ Change (T1-T2), P = 0.550 Spasticity of knee flexors in 35 patients with CP during different stages of CITB treatment: • MAS knee flexors right, Median (range): ◦ Baseline (T0); 4.0 (2 to 6) ◦ 6 months (T1); 4.0 (2 to 6) ◦ 18 months (T2); 3.0 (1 to 6) ◦ Change (T0 - T1), P = 0.627 ◦ Change (T0 - T2), P = 0.022 ◦ Change (T1-T2), P = 0.062

Outcome measures/ Effect size	• MAS knee flexors left, Median (range): ◦ Baseline (T0); 4.0 (2 to 6) ◦ 6 months (T1); 3.5 (2 to 6) ◦ 18 months (T2); 3.0 (1 to 6) ◦ Change (T0 - T1), P = 0.353 ◦ Change (T0 - T2), P = 0.022 ◦ Change (T1-T2), P = 0.062 PEDI and GMFM-66 in 35 patients with CP during different stages of CITB treatment: • GMFM-66 total score , Median (range): ◦ Baseline (T0); 22.7 (0.0 to 48.3) ◦ 6 months (T1); 22.0 (0.0 to 45.9) ◦ 18 months (T2); 24.0 (0.0 to 47.1) ◦ Change (T0 - T1), P = 0.032 ◦ Change (T0 - T2), P = 0.005 ◦ Change (T1-T2), P = 0.064 PEDI Functional skills (Scaled scores) Median (range): • Self-care ◦ Baseline (T0); 33.6 (0.0 to 58.6) ◦ 6 months (T1); 33.0 (0.0 to 61.8) ◦ 18 months (T2); 36.0 (0.0 to 73.6) ◦ Change (T0 - T1), P = 0.246 ◦ Change (T0 - T2), P = 0.027 ◦ Change (T1-T2), P = 0.124 • Mobility ◦ Baseline (T0); 23.2 (0.0 to 53.1) ◦ 6 months (T1); 20.9 (0.0 to 48.8) ◦ 18 months (T2); 35.9 (0.0 to 54.8) ◦ Change (T0 - T1), P = 0.285 ◦ Change (T0 - T2), P = 0.017 ◦ Change (T1-T2), P = 0.012 • Social function ◦ Baseline (T0); 57.9 (0.0 to 96.3) ◦ 6 months (T1); 59.2 (0.0 to 96.3) ◦ 18 months (T2);64.1 (0.0 to 100.0) ◦ Change (T0 - T1), P = 0.041 ◦ Change (T0 - T2), P = 0.002 ◦ Change (T1-T2), P = 0.035 PEDI Caregiver assistance (Scaled scores), Median (range): • Self-care ◦ Baseline (T0); 15.9 (0.0 to 57.9) ◦ 6 months (T1); 11.6 (0.0 to 63.4) ◦ 18 months (T2); 11.6 (0.0 to 76.7) ◦ Change (T0 - T1), P = 1.000 ◦ Change (T0 - T2), P = 0.272 ◦ Change (T1-T2), P = 0.678 • Mobility ◦ Baseline (T0); 11.7 (0.0 to 70.5) ◦ 6 months (T1); 29.0 (0.0 to 58.8) ◦ 18 months (T2);36.9 (0.0 to 72.7) ◦ Change (T0 - T1), P = 0.066 ◦ Change (T0 - T2), P = 0.008 ◦ Change (T1-T2), P = 0.034 • Social function ◦ Baseline (T0); 58.3 (0.0 to 100.0) ◦ 6 months (T1); 66.9 (0.0 to 100.0) ◦ 18 months (T2); 65.9 (0.0 to 100.0) ◦ Change (T0 - T1), P = 0.035 ◦ Change (T0 - T2), P = 0.004 ◦ Change (T1-T2), P = 0.025 **Authors conclusion** The authors concluded that there seems to be a sequence of changes after introduction of continuous intrathecal baclofen in a child with cerebral palsy that may guide the multi disciplinary team in their timing of therapy during post-surgical follow-up.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	14. Gluglielmino A, Sorbello M, Fazzio S, Zingale SF, Bucolo GE, Pittala G, Castiglione A, Patti F, Mangiamfli S. Continuous intrathecal baclofen administration by a fully implantable electronic pump for severe spasticity treatment: our experience. Minerva Anestesiol. 2006;72:807-820
Study Type / Methods	Pre and post intervention study conducted at the University Hospital of Catania, Italy. The aim of the study was to evaluate the efficacy of continuous intrathecal baclofen infusion delivery by a programmable pump for severe spasticity according to patient selection criteria, implantation technique and related parameters, and outcome after the initial follow-up period. Intrathecal baclofen infusion was initiated in 30 patients within 24 hour after a test dose of the agent resulted positive in spinal anaesthesia. During the procedure and the follow-up period, the following parameters were measured: incidence of anaesthesiological or surgical complications and adverse events, postdural puncture headache, prolonged motor block, difficulty in wound healing, infection, necessity to remove the pump; clinical response as measured on the Ashworth and spasms scales, quality of sleep, autonomy, quality of life and pain before and after intrathecal baclofen therapy.
LE	II-2
Number of Patients and Patient Characteristics	30 patients: • Male to female ratio; 2:1 • Mean age; 51 ± 4.3 years, range (36 to 67 years) • Mean duration of symptoms; 6 years, range (1 to 3 years) Origin of spasticity: • Multiple sclerosis (73.4%) • Lateral amyotrophic sclerosis (3.3%) • Spine lesions (10%) • Spine tumours (6.7%) • Spastic paresis (3.3%) • Other (3.3%) Inclusion criteria: • Medical therapy failure • Ashworth score ≥ 3 • Spasm score ≥ 2 • Age ≥ 16 • ITB test positivity ≤ 100 µg • Severe spine deformity
Intervention	Continuous ITB infusion Programmable pumps (Synchromed Infusion System)
Comparison	No comparator
Length of follow up (if applicable)	8 months
Outcome measures/ Effect size	Changes in Pre and Post ITB treatment: • Ashworth score , Mean ± SD: ◦ Pre ITB; 4.3 ± 0.6 ◦ Post ITB; 1.2 ± 0.3 ◦ Change (Post ITB - Pre ITB), P < 0.0005 • Spasm score , Mean ± SD: ◦ Pre ITB; 3.1 ± 1.1 ◦ Post ITB; 0.7 ± 0.4 ◦ Change (Post ITB - Pre ITB), P < 0.0005 • Quality of sleep , Mean ± SD: ◦ Pre ITB; 2 ◦ Post ITB; 4 ◦ Change (Post ITB - Pre ITB), P < 0.01 • Autonomy, Mean ± SD: ◦ Pre ITB; 1 ◦ Post ITB; 3 ◦ Change (Post ITB - Pre ITB), P < 0.01 • Quality of Life, Mean ± SD: ◦ Pre ITB; 2 ◦ Post ITB; 4 ◦ Change (Post ITB - Pre ITB), P < 0.01 • VAS pain score , Mean ± SD: ◦ Pre ITB; 6.2 ± 2.1 ◦ Post ITB; 3.3 ± 1.74 ◦ Change (Post ITB - Pre ITB), P < 0.005 Mean duration of the operation; 86 ± 13 minutes Mean length of stay from the test day until discharge; 8 ± 2 days (range, 6 to 17 days). **Authors conclusion** The authors concluded that the good clinical response to treatment of spasticity and rigidity, improved quality of life, pain reduction and patient satisfaction with short length of admission demonstrate the efficacy of intrathecal baclofen therapy. Safe and efficacious, this mode of treatment appears to be the gold standard for treating severe spasticity.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	15. Francisco GE, Hu MM, Boake C, Ivanhoe CB. Efficacy of early use of intrathecal baclofen therapy for treating spastic hypertonia due to acquired brain injury. Brain Injury. 2005;19(5):359-364
Study Type / Methods	Pre and post intervention study conducted at University of Texas Health Sciences Centre, Houston, TX, USA. The aim of the study was to determine the efficacy and safety of early (< 1 year post-disease onset) use of intrathecal baclofen (ITB). A consecutive series of 14 individuals with acquired brain injury (ABI) who received ITB within 1 year of disease onset were identified from the ITB database of spastic hypertonia management programme at the centre. In each patient, spastic hypertonia was recalcitrant to other treatment modalities. Intrathecal baclofen trial was performed and patients who had positive response were admitted for pump placement. The Modified Ashworth Scale (MAS) was the primary outcome measure. The Disability Rating Scale (DRS) score was the secondary outcome measure. The DRS rates eight sub scales measuring level of consciousness, cognitive independence in self-care, employability and the need for supervision and subscale ratings are summed to yield a total score (range 0 = no disability to 29 = vegetative state; death = 30).
LE	II-2
Number of Patients and Patient Characteristics	14 patients: • 6 males, 8 females • Mean age was 35.9 years, range (9 to 65 years) Diagnosis: • Anoxic encephalopathy (6 patients) • Traumatic brain injury (TBI) in 5 patients • Stroke (3 patients)
Intervention	Continuous ITB infusion Programmable pumps (Synchromed Infusion System)
Comparison	No comparator
Length of follow up (if applicable)	Mean of 13.9 months post ITB implantation
Outcome measures/ Effect size	Changes in baseline and follow-up treatment: Modified Ashworth scale (MAS), Mean ± SD: • Mean MAS scores dropped by 1.0, SD 1.4, P < 0.02 for upper extremities • Mean MAS scores dropped by 2.1, SD 1.4, P < 0.001 for lower extremities DRS scores: DRS scores changed from an average of 17.6 (SD, 5.1) before to 15.6 (SD, 6.7) after ITB therapy. The change in DRS scores was not significant (P = 0.75) Functional Gains: Functional gains observed included decreased pain, improved activities of daily living, improved range of motion, improved motor skills, decreased primitive reflexes and faster gait speed. These gains were noted on the basis of informal observation, since motor function other than spasticity was not formally measured. ITB Dose: Spastic hypertonia was considered controlled when it did not interfere with transfer, mobility, hygiene and activities of daily living and the patient was able to participate in more therapies. To achieve this level of control, patients required a mean daily ITB dose of 591.5 µg with the range of 93 to 2000.2 µg per day at the time of most recent follow-up. **Authors conclusion** ITB therapy within 1 year of onset of acquired brain injury appears effective and safe in decreasing spastic hypertonia and does not appear to adversely affect recovery.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	16. Guillaume D, Van Havenbergh A, Vloeberghs M, Vidal J, Roeste G. A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity. Arch Pys Med Rehabil. 2005;86(11):2165-2171
Study Type / Methods	Non comparative prospective cohort (pre and post intervention study) conducted at 24 centres in Austria, Belgium, Denmark, Germany, Luxembourg, Norway, Sapain, Sweden, Switzerland, and United Kingdom from December 1998 to December 2000. The aim of the study was to determine the impact of intrathecal baclofen (ITB) therapy on outcomes of functional independence, pain, subjective improvement, performance, and standard measures of spasticity. Clinical outcome data were collected for patients with intractable spasticity of either spinal or cerebral origin who received ITB therapy at centres in Europe. Study participants underwent a screening trial to assess their responses to ITB. Programmable pumps (Synchromed Infusion System) were implanted in patients who responded positively to the ITB trial. Spasticity in the lower and upper extremities was evaluated at entry, 3,6,9 and 12 months post implantation using Ashworth Scale assessment of muscle tone. Spasm scores was measured by Penn Spasm Frequency Scale (PSFS). Pain assessment using numeric rating scale (NRS), where patients were asked to evaluate their pain using a numeric rating (0 = no pain, to 10 = the worst pain imaginable). Motor and cognitive functions were evaluated using FIM instrument or WeeFIM for children. Patient performance and satisfaction with 1 to 5 tasks selected by themselves or their caregivers at study entry were measured on the Canadian Occupational Performance Measure (COPM). The instrument measures changes in a patient's self-perception of personal performance of specific tasks over time. Subjective ratings (very poor, poor, fair, good, very good) of overall relief from spasticity and pain with current treatments were obtained from patients and physicians at the study entry and at the 4 follow-up visits. Safety evaluations were recorded at each visit throughout the study.
LE	II-2
Number of Patients and Patient Characteristics	129 patients: • 64 % males • 36 % females • Mean age was 35.2 ± 18.8 years, range (4 to 74 years) Aetiology of spasticity (%): • Multiple sclerosis (MS) - 30% • Spinal cord injury (SCI) - 26% • Cerebral palsy (CP) - 24% • Traumatic brain injury (TBI) - 7% • Stroke (2%) • Other (11%) Inclusion criteria: • Patients between 5 and 75 years of age
Intervention	Continuous ITB infusion Programmable pumps (Synchromed Infusion System)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in baseline, 3 and 12 of treatment: Ashworth Assessments, Mean ± SD Cerebral –origin spasticity • Lower extremities: ◦ Baseline, 4.02 ± 0.92 ◦ Month 12, 1.96 ± 0.78 ◦ P < 0.001 • Upper extremities: ◦ Baseline, 3.58 ± 1.25 ◦ Month 12, 2.07 ± 0.86 ◦ P < 0.001 Spinal –origin spasticity • Lower extremities: ◦ Baseline, 3.68 ± 0.81 ◦ Month 12, 1.92 ± 0.75 ◦ P < 0.001 • Upper extremities: ◦ Baseline, 1.65 ± 0.78 ◦ Month 12, 1.34 ± 0.50 ◦ P < 0.001

Penn spasm Frequency Scale scores, Mean ± SD

- Baseline, 2.70 ± 1.24
- Month 12, 0.72 ± 0.95
- P < 0.001 Pain assessment

- Patients' pain assessments during follow-up showed significant (P < 0.001) reductions in pain after implantation in all 4 categories (worst pain, least pain, average pain, current pain) at all 4 visits
- Pain relief increased steadily over the 12 months of follow-up for worst pain in the previous week, average pain in the previous week, and current pain whereas the least-pain ratings remained at a similar level at the 4 time points after the initial decrease

Motor and cognitive functions (Average FIM and WeeFIM Scores, Mean ± SD)

Cerebral –origin spasticity

- Motor function:
  - Baseline, 38.3 ± 25.1
  - Month 3, 40.7 ± 26.7, P = 0.081
  - Month 12, 42.7 ± 27.7, P < 0.001

- Cognitive function:
  - Baseline, 26.6 ± 11.3
  - Month 3, 27.1 ± 10.9 , P = 0.010
  - Month 12, 27.6 ± 10.4, P < 0.059

- Overall score:
  - Baseline, 64.3 ± 34.0
  - Month 3, 67.9 ± 35.2 , P = 0.034
  - Month 12, 69.8 ± 36.0, P < 0.001

- Canadian Occupational Performance Measure (COPM):
  - The COPM assessments at 3 and 12 months post implantation showed significant (P< 0.001) improvements in performance and satisfaction in selected occupational tasks as perceived by the patients

- Subjective ratings by patients and physicians on spasticity and pain:
  - Patients reported significantly (P < 0.001) improved ratings of spasticity and pain relief after initiation of ITB therapy compared with pretherapy ratings. Physicians reported similar results.
  - At baseline, 6% of patients rated spasticity relief as good or very good. After initiation of baclofen therapy, spasticity relief was rated as good or very good by 69% of patients at 3 months and 84% at 12 months. At baseline, 2% of physicians rated their patient's spasticity relief as good or very good. After 12 months of therapy, physicians rated spasticity relief as good or very good in 89% of those patients.
  - At baseline, 12% of patients rated pain relief as good or very good compared with 70% after 12 months of ITB treatment. At baseline, 9% of patients were rated by their physicians as having pain relief that was good or very good compared to 72% at 12 months.

ITB Dose:

The mean starting dose of ITB was 129 µg/day. At 12 month visit, the mean baclofen dose had increased to 288 µg/day.

Authors conclusion

ITB therapy using a programmable pump is clinically effective and well tolerated, despite a seemingly high level of adverse events. In patients with intractable spasticity of spinal or cerebral origin and may offer improvements in pain relief and function.

General comments

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	17. Boviatsis EJ, Kouyialis AT, Korfias S, Sakas DE. Functional outcome of intrathecal baclofen administration for severe spasticity. Clinical Neurology and Neurosurgery. 2005;107:289-295
Study Type / Methods	Pre and post intervention study conducted at the University of Athens Medical School, Greece. The aim of the study was to estimate the functional benefit in patients with severe spasticity treated with intrathecal baclofen infusion through an implantable pump and to stress the need for functional assessment of these patients with a functional scale. Between 1999 and 2003, 22 patients with a long history of severe and disabling pharmaceutically intractable spasticity, underwent implantation of a pump for continuous intrathecal baclofen infusion. The patients were subdivided into two categories according to the aetiology of spasticity; 15 had Multiple Sclerosis and seven suffered a Spinal Cord Injury at different levels (from C4 to T11). Clinical status was assessed with Ashworth and Penn spasm scales. Functional benefits were evaluated with the Barthel index score and pain relief with a self-reported visual analogue pain scale.
LE	II-2
Number of Patients and Patient Characteristics	22 patients: • 12 males, 10 females • Average age was 44.7 years, range (27 to 63 • Average disease duration was 12.04 years (range 1 to 30 years, median 12 years). Diagnosis: • 15 had multiple sclerosis (6 immobile, 4 wheelchair independent, 4 could walk with help) • 7 had spinal cord injury (4 paraplegic, none able to walk) Inclusion criteria: • Chronic disabling spasticity (score ≥ 4 in Ashworth scale • Failure of per oral antispastic drugs after administration of maximum tolerated or recommended doses • Duration of symptoms > 12 months • Absence of block in CSF circulation • No allergy to medication • Age < 65 years • Positive response to bolus intrathecal baclofen administration
Intervention	Continuous ITB infusion Infusion pump
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up of 32 months (range, 9 to 55 months, median 35 months)
Outcome measures/ Effect size	Changes in baseline and follow-up treatment: Multiple sclerosis (MS) group • Ashworth scale scores, Mean ± SD: ◦ At last follow-up, the mean Ashworth score had decreased 2.33 points (from 4.4 to 2.07, P < 0.0001) • Penn spasm scores: ◦ Reduction of 1.78 points (from 3.28 to 1.5, P < 0.001) • Functional outcome [Barthel index score (BIS)]: ◦ Preoperative average BIS for the MS patients were 34.64, ranging from 10 to 65 (median=35). After the procedure, there was an overall functional status improvement expressed by a BIS increase to 62.85 ranging from 10 to 95 (median = 65), P < 0.022). Amount of improvement was different for different activities. Activities that required reduction of spasticity at the lower limbs such as transfers, mobility and stair climbing, showed statistically significant improvement (P = 0.0018, 0.0004 and 0.0011, respectively). Post operatively, 3 immobile patients became wheelchair independent,5 could walk with help and 4 became independently ambulatory • Self assessment pain scale: ◦ The average preoperative pain score was 6.42/10 (median = 6) and was reduced to 1.78/10 (median = 0.5, P = 0.0007) with 6 patients reported complete relief. Spinal cord injury group • Ashworth scale score, Mean ± SD: ◦ At last follow-up, the mean Ashworth score had decreased 2.0 points (from 4.57 to 2.57, P = 0.0134) • Penn spasm scores: ◦ Reduction of 2.43 points (from 3.71 to 1.28, P = 0.00006) • Functional outcome [Barthel index score (BIS)]: ◦ Preoperative average BIS for the SCI patients were 17.1, ranging from 0 to 45 (median = 15). After the procedure, there was an overall functional status improvement expressed by a BIS increase to 50.7 ranging from 5 to 90 (median = 50), P <0.073). Activities in which improvement reached statistical significance were dressing (P = 0.04650 and transfers (P = 0.0016). ◦ Post operatively, 2 became ambulatory with or without assistance, and 2 became wheelchair independent. Reported improvement in transferring to or from the wheelchair, for dressing upper and lower body and toilet use with minor help or independently. • Self assessment pain scale: ◦ Three reporting improvement, one noticing no changes, (P = 0.0941). No increase in pain was noted. **Authors conclusion** Reduction of spasticity and spasms achieved with intrathecally delivered baclofen, leads to functional improvement and pain relief.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	18. Awaad Y, Tayem H, Munoz S, Ham S, Michon Am, Awaad R. Functional assessment following intrathecal baclofen therapy in children with spastic cerebral palsy. J Child Neurol. 2003;18:26-34
Study Type / Methods	Pre and post intervention study conducted at the Children's Hospital of Michigan, Wayne State University, School of Medicine, Detroit. The aim of the study was to describe the outcomes of a series of patients with cerebral palsy who received intrathecal baclofen to reduce spasticity. After being identified as appropriate candidates for intrathecal baclofen therapy, each patient underwent a screening trial with 50 g bolus intrathecal injection of baclofen into the lumbar region. After a positive response and pump implantation, patients were asked for follow-up assessments at 1, 6, 12, 18 and 24 months. The patients received individualised rehabilitation, including physical and occupational therapies, speech therapy, and gait training, to maximise the functional effects of the drug. The Ashworth Scale was used as a clinical measure of impairment and the Paediatric Evaluation of Disability Inventory (PEDI) was used to assess the dimensions of functional limitations and disability. In addition groups were formed for analysis by age and level of functional mobility. Foe age, group 1 included subjects less than 18 years and group 2 consisted subjects 18 years of age or older. For functional mobility, the low mobility group consisted of subjects with baseline PEDI mobility raw scores of 0 to 15 points, and high mobility group had baseline raw scores of 21 to 54 points.
LE	II-2
Number of Patients and Patient Characteristics	39 patients: • 27 males, 12 females • Mean age was 13.69 years, SD (7.43 years), range 4 to 32 years Baseline data [Mean (SD), range]: • Ashworth scale score, = 3.25 (0.58), 2.3 to 4.8 • PEDI functional skills: mobility = 25.44 (20.41), 0 to 79.8 Inclusion criteria: • At least 4 years of age • Weigh > 30 pounds • Severe spasticity in the lower extremities (average Ashworth Scale score at least 3 in lower extremities • Undergo a trial of oral antispasmodic agent for at least 6 months
Intervention	Continuous ITB infusion and individualised rehabilitation programme Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	24 months
Outcome measures/ Effect size	Changes in baseline and follow-up treatment: • Ashworth scale scores: [Mean (SD), Change from baseline; Mean (SD), P value] ◦ Before trial, 3.26 (0.61), ◦ 1 month, 1.78 (0.52), 1.55 (0.72), P< 0.0005 ◦ 6 months, 1.64 (0.59), 1.67 (0.85), P< 0.0005 ◦ 12 months, 1.61 (0.58), 1.67 (0.74), P< 0.0005 ◦ 18 months, 1.60 (0.49), 1.73 (0.87), P< 0.0005 All Functional skills and caregiver assistance improved. • PEDI Functional skills: Self-Care Domain scores: [Mean (SD), Change from baseline; Mean (SD), P value] ◦ 6 months, 37.90 (24.35), + 5.71 (11.00), P= 0.014 ◦ 12 months,37.90 (26.04), + 5.60 (10.55), P= 0.016 ◦ 18 months,37.91 (29.00), + 6.27 (10.65), P= 0.020 • PEDI Functional skills: Social Function Domain scores: [Mean (SD), Change from baseline; Mean (SD), P value] ◦ 6 months, 47.92 (23.03), + 5.98 (10.28), P= 0.007 ◦ 12 months,46.94 (23.13), + 5.45 (10.41), P= 0.017 ◦ 18 months,46.15 (26.58), + 5.16 (11.39), P= 0.064 • There were no significant findings in the mobility functional skills domain as most of the patients were quadriplegic • PEDI Caregiver Assistances: Mobility Domain scores: [Mean (SD), Change from baseline; Mean (SD), P value] ◦ 6 months, 26.08 (28.66), + 10.82(19.65), P= 0.010 ◦ 12 months,36.88 (33.75), + 9.96 (17.23), P= 0.009 ◦ 18 months,30.73 (36.23), +11.61(16.72), P= 0.007 • Comparing groups of adults and patients less than 18 years, there were no significant differences, but there was a relationship between age and dose. • Comparing groups of patients in high and low levels of independent functional mobility, no significant differences were found. **Authors conclusion** These results provide suggestive evidence that the combination of intrathecal baclofen therapy and rehabilitation has positive effects across the dimensions of disablement.
General comments	

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Bibliographic Citation	19. Murphy NA, Nicole Irwin MC, Hoff C. Intrathecal baclofen therapy in children with cerebral palsy: efficacy and complications. Arch Phys Med Rehabil. 2002;83:1721-1725
Study Type / Methods	Pre and post intervention study conducted at the University of Utah, Salt Lake City between March 1997 and Mach 2001. The aim of the study was to describe the efficacy of intrathecal baclofen (ITB) therapy in the management of spasticity in young children with cerebral palsy (CP) and to identify risk factors for complications. Candidates for ITB were identified, and each child participated in a screening trial. All 25 ITB delivery systems implanted in 23 children during the 48 month study period were reviewed. Average upper-and lower-extremity Ashworth Scale scores were assessed at baseline and after 6 and 12 months of ITB. To explore the differences between the children who required explanation of the ITB delivery system with those who did not, a series of t tests and chi-square analyses were performed.
LE	II-2
Number of Patients and Patient Characteristics	23 children with severe spasticity secondary to CP: • 17 boys, 6 girls. • Age ranged from 4.5 to 17.4 years, with an average of 8.8 years and a median ± standard deviation (SD) of 7.4 ± 3.9 years. • Spastic diplegia present in 22% (5/23) • Spastic quadriplegia in 61% (14/23) • Mixed-type (extrapyramidal and spastic features) in 4% (1/23) • Mixed type quadriplegia in 13% (3/23)
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in baseline and follow-up treatment: Lower extremity • (Average Ashworth scale scores ± SD): ◦ 3.26 ± 0.73 at baseline, decreased to 2.34 ± 0.83 at 6 months ($P \leq 0.01$) and at 12 months, it was 2.43 ± 0.73. Upper extremity • (Average Ashworth scale scores ± SD): ◦ 2.69 ± 0.79 at baseline, decreased to 2.00 ± 0.55 at 6 months ($P \leq 0.05$) and at 12 months, it was 2.07 ± 0.65. **Authors conclusion** ITB therapy effectively reduced spasticity in children with CP. However, complications necessitating ex-plantation can occur. Further research is needed to identify criteria describing the ideal paediatric candidate for ITB.
General comments	

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Bibliographic Citation	20. Dario A, Di Stefano MG, Grossi A, Casagrande F, Bono G. Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. Acta Neurol Scand. 2002;105:83-87
Study Type / Methods	Pre and post intervention study conducted in Italy. The aim of the study was to evaluate long-term results of chronic intrathecal baclofen infusion on the spasticity, on the spasms and to evaluate the side-effects of the intrathecal baclofen in patients with supraspinal spasticity. Fourteen patients with severe progressive refractory to medical therapy spasticity were evaluated after chronic intrathecal baclofen infusion performed by implantation of subcutaneous programmable pump. The patients had suffered traumatic or anoxic acquired brain injuries. The clinical evaluation was made using Ashworth Scale (AS) and the Spasm Frequency Scale (SFS). The parameters were assessed before intrathecal therapy, 3, 6, 12 hour after bolus administration of intrathecal baclofen and every 6 months after pump implantation.
LE	II-2
Number of Patients and Patient Characteristics	14 patients: • 10 males, 4 females • Mean age was 38.8 years (range; 18 to 56 years) • Glasgow Outcome Scale (GOS) score before administration of intrathecal baclofen was 2 in eight patients and 3 in six patients. • History of post injury spasticity was at least 6 months with a mean of 36.7 months
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean of 23.5 months after implantation (range 6 to 65 months)
Outcome measures/ Effect size	Changes in baseline (preoperative) and at last follow-up treatment: Lower extremity • (Ashworth scale scores, Mean ± SD): ◦ At last follow-up decreased from preoperative value of 4.3 ± 0.5 to a postoperative value of 2.7 ± 0.7, $P < 0.05$ Upper extremity • (Ashworth scale scores, Mean ± SD): ◦ At last follow-up decreased from preoperative value of 4.1 ± 0.8 to a postoperative value of 2.3 ± 0.9, $P < 0.05$ • Spasm Frequency Scale (SFS) score (Mean ± SD): ◦ At last follow-up decreased from preoperative value of 2.5 ± 0.5 to a postoperative value of 0.4 ± 0.6, $P < 0.001$ Baclofen dosage: • After implantation 12 patients needed a progressive increase of the baclofen infusion, whereas in a patient one year after surgery it was possible to decrease the drug infusion. The mean daily dose of baclofen was 305 µg (range 90 to 510 µg). **Authors conclusion** The intrathecal infusion of baclofen seems to be an effective treatment in patients with supraspinal spasticity.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	21. Dario A, Scamoni C, Bono G, Ghezzi A, Zaffaroni M. Functional improvement in patients with severe spinal spasticity treated with chronic intrathecal baclofen infusion. Functional Neurology. 2001;16: 311-315
Study Type / Methods	Pre and post intervention study conducted in Italy. The aim of the study was to evaluate the efficacy and functional benefits of chronic intrathecal baclofen infusion in severe spinal spasticity. Twenty patients with a diagnosis of severe intractable spinal spasticity were evaluated prior to implantation of a programmable pump for chronic intrathecal baclofen therapy and at follow-up, which ranged from 12 to 36 months (mean 22.4 months). Patient assessment was based on Ashworth Scale to assess spasticity, four-point Spasm Frequency Scale to assess spasm, self-reported pain and Functional Independence Measure (FIM) scores to assess physical disability. The Wilcoxon test was used for statistical analyses.
LE	II-2
Number of Patients and Patient Characteristics	20 patients: • 9 males, 11 females • Mean age was 39.8 years (range; 27 to 52 years) • Clinical history of spasticity had a duration of at least 12 months (mean; 36.5 months) • All patients were unable to walk • Causes of spasticity: ◦ Multiple sclerosis (n = 13) ◦ Trauma (n = 4) ◦ Spinal tumours (n = 2) ◦ spinal myelitis (n =1) • All patients but 2 had spastic paraparesis
Intervention	Continuous ITB infusion. Continuous infusion pump (SynchroMed, Medtronic)
Comparison	No comparator
Length of follow up (if applicable)	Mean of 22.4 months after implantation (range 12 to 36 months)
Outcome measures/ Effect size	Changes in baseline (preoperative) and at last follow-up treatment: • Ashworth scale score (Mean ± SD): ◦ At last follow-up decreased from preoperative value of 4.4 ± 0.5 to a postoperative value of 1.8 ± 0.7, $P < 0.01$ • Spasm Frequency Scale (SFS) score (Mean ± SD): ◦ At last follow-up decreased from preoperative value of 2.5 ± 0.8 to a postoperative value of 0.5 ± 0.4, $P < 0.01$ • Self-reported pain score: ◦ At last follow-up decreased from preoperative score of 5.5 ± 2.2 to a postoperative score of 2.3 ± 1.9, $P < 0.05$ • Functional Independence Measure (FIM) score (Mean ± SD): ◦ A statistically significant change in the FIM score was observed (an increased from preoperative mean score of 33.8 ± 6.9 to a postoperative mean score of 58.7 ± 10.4, $P < 0.05$). In particular the improvement regarded items; bathing, dressing the lower body and transferring of the body. ◦ Two patients in employment were able to resume work • Baclofen dosage: ◦ The mean daily dose of baclofen was 295 µg (range 90 to 830 µg).
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	22. Korenkov AI, Niendorf WR, Darwish N, Glaeser E, Gaab MR. Continuous intrathecal infusion of balcofen in patients with spasticity caused by spinal cord injuries. Neurosurg Rev. 2002;25:228-230
Study Type / Methods	Pre and post intervention study conducted in Germany. The aim of the study was to determine the efficacy and safety of intrathecal baclofen therapy delivered by a programmable pump for the chronic treatment of spinal spasticity. Twelve patients with intractable spasticity caused by spinal cord injuries underwent implantation of a programmable continuous infusion pump after significant reduction in spasticity following an intrathecal test bolus of baclofen. Patients were examined 2 weeks after pump implantation and subsequently every 2 to 3 months for pump refill. The infusion rate and infusion mode were adjusted by telemetry using a briefcase-sized programmable computer. Spasticity was measured according to the degree of rigidity (Ashworth scale) and by means of a spasm frequency score in the preoperative and post-operative periods.
LE	II-2
Number of Patients and Patient Characteristics	12 male patients with spastic quadriparesis and spastic paraplegia caused by spinal cord injuries
Intervention	Continuous ITB infusion. Programmable continuous infusion pump (SynchroMed, Medtronic)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in baseline (preoperative) and at last follow-up treatment: **Ashworth scale score (Mean):** • Lower limbs ◦ At last follow-up decreased from preoperative value of 4.2 to a postoperative value of 2.2, $P < 0.05$ • Upper limbs ◦ At last follow-up decreased from preoperative value of 2.2 to a postoperative value of 1.0, $P < 0.05$ • Spasm Frequency Scale (SFS) score (Mean): ◦ At last follow-up decreased from preoperative value of 2.8 to postoperative value of 1.0, $P < 0.05$ • Quality of life: ◦ Observed improvement of quality of life in all patients. Self-care, nursing care, and physiotherapy became easier. Transfer from wheelchair to bed was easier and patients were able to sit for longer periods of time. Muscle pain and sleeplessness improved. **Authors conclusion** The surgical procedure of pump and catheter implantation is simple and associated with few complications. Chronic intrathecal baclofen administered by an implanted programmable pump is a non-destructive, safe, and effective method of treatment of intractable spasticity due to spinal cord injury. The use of a programmable pump allows non invasive interrogation and programming of implanted pumps and hence a reduction in the risk of infections.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	23. Campbell WM, Ferrel A, McLaughlin JF, Grant GA, Loeser JD, Graubert C, Bjornson K. Long-term safety and efficacy of continuous intrathecal baclofen. Developmental Medicine & Child Neurology. 2002;44:660-665
Study Type / Methods	Retrospective review of a pre and post intervention study and cross-sectional survey at Children's Hospital and Regional Medical Centre (CHRMC), Seattle, WA, USA. The aim of the study was to report on the long-term safety and efficacy of continuous intrathecal baclofen (CITB) infusion in the treatment of 21 children with intractable severe spasticity of cerebral origin. The study was based on a retrospective review of collected data in patient files and a computer database, and a prospective telephone survey. The cross-sectional survey was performed in 1999. All 21 consecutive children and adolescents who began CITB at CHRMC between December 1994 and December 1998 were included. All recipients had a successful test dose of intrathecal baclofen (50 or 100 µg) as inpatients before elective placement of the baclofen pump. Individual treatment goals were set preoperatively. The recipients were scheduled to return to the neurosurgery clinic at CHRM every 1 to 3 months for pump refill and to the Spasticity Management Clinic at 6 and 12 months after implantation where various outcomes were measured which include Ashworth scale, Gross Motor Function Measure (GMFM) and Paediatric Evaluation of Disability Inventory (PEDI). To describe more completely the benefits, adverse events, and family satisfaction with CITB, a semi-structured telephone survey was conducted for 17 recipients' stills receiving this treatment in July 1999.
LE	II-2
Number of Patients and Patient Characteristics	21 children • 15 males, 6 females • 7 had level IV severity of Gross motor Functional Classification System • 14 had level V severity of Gross motor Functional Classification System • 19 had spastic quadriplegia, 2 had spastic diplegia • All were wheelchair users • 13 had clinical athetosis or dystonia as a secondary component of their disorder
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	31 to 78 months; (mean 53 months SD; 4 months)
Outcome measures/ Effect size	Changes in baseline (preoperative) and at 6 months follow-up treatment: Ashworth scale score (Mean (SD)]: • Lower limbs ◦ Mean Ashworth lower extremity scores improved by 1.3 points (SD; 0.5) between baseline and 6-month follow-up in the 14 recipients with follow-up scores • Upper limbs ◦ Reduction in upper extremity spasticity was seen to a smaller but still important extent. Mean Ashworth upper extremity scores improved by 0.8 points (SD; 0.7) between baseline and 6-month follow-up in the 14 recipients with follow-up scores • Functional Measures ◦ The GMFM showed no functional change for most of the 17 recipients with baseline and follow-up scores. Two recipients showed functional improvements in the lying / rolling and sitting dimensions, and one of these improved in the crawling / kneeling dimension. ◦ The PEDI also showed few functional changes in the eight recipients with follow-up scores. In the PEDI mobility domain, two recipients improved in the care-assist dimension, and one recipient improved in the modifications dimension. • Qualitative Measures Attainment of treatment goals: ◦ Of 108 initial treatment goals, 101 (94%) were at least partly achieved and 78 (72%) were completely or almost completely achieved by July 1999. Treatment goals included improvement in function (independent mobility and self-help skills), comfort (pain reduction and being able to sleep better and sit longer), and care-giving (dressing and positioning). All families interviewed identified some goals that were achieved. • Other reported benefits ◦ Improved sleep noted in 4 recipients ◦ Improved supported or assisted standing reported in 4 recipients ◦ Improved hand function reported in 2 recipients ◦ Better control of an electric wheelchair reported in 1 recipient ◦ Of the ten recipients treated with oral antispasticity medications before pump implantation, medications were discontinued in 7 and reduced in 3 ◦ 34 additional treatment benefits were reported that had not been documented as the original treatment goals which included increased comfort, decreased pain, and improvements in mobility and daily living skills • Caregiver satisfaction ◦ Of 17 caregivers, 16 stated that they 'would go through it again', 14 stated that they 'would have the pump replaced', 2 were undecided, and 1 would not have the pump replaced because of the child's fear of needles at the time of refill. ◦ 15 of 17 caregivers would recommend CITB to others and 14 reported that they had actually done so.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	24. Meythaler JM, Guin-Renfroe S, Law C, Grabb P, Hadley MN. Continuously infused intrathecal baclofen over 12 months for spastic hypertonia in adolescents and adults with cerebral palsy. Arch Phys Rehabil. 2001;82:155-161
Study Type / Methods	Pre and post intervention study at the University Alabama School of Medicine, Birmingham, Alabama. The aim of the study was to determine if the continuous intrathecal delivery of baclofen will control spastic hypertonia caused by long standing cerebral palsy (CP). Thirteen CP patients with intractable spastic hypertonia and quadriparesis who had not responded to oral medications including baclofen were screened via a bolus injection of baclofen intrathecally. Those who dropped an average of 2 points on the their lower extremity (LE) Ashworth scores were offered computer-controlled pump implantation for 12 months of continuous delivery of intrathecal baclofen (ITB). Ashworth rigidity scores, spasm scores and deep tendon reflex scores were collected for both the upper extremities (UEs) and LES. Differences over time were assessed via descriptive statistics and Wilcoxon's signed rank test. Patients were scheduled for data collection at 1, 3, 6, 9 months and 1-year post pump placement.
LE	II-2
Number of Patients and Patient Characteristics	13 cerebral palsy patients: • 10 men, 3 women • Average age was 25 years (range; 13 to 43 years) • 13 had disabling LE spastic hypertonia • 12 had UE spastic hypertonia, and 1 patient had spastic diplegia Inclusion criteria: • Older than 13 years of age • Diagnosis of severe chronic spastic hypertonia in lower extremities (Ashworth score of at least 3 in the affected extremities) • Failure to respond satisfactorily to treatment with oral antispasticity medications
Intervention	Continuous ITB infusion Programmable pump device
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in baseline (preoperative) and at 1 year follow-up treatment: • Lower extremities (LE): ◦ After 1 year of continuous ITB, the average LE Ashworth score (Mean± SD) decreased 1.9 points from 3.4 ± 1.2 before treatment to 1.5 ± 0.7 after 12 months post treatment , $P < 0.0001$ ◦ Average LE spasm score (Mean ± SD) decreased 0.8 points from 1.4 ± 1.6 before treatment to 0.6 ± 1.2 after 12 months post treatment , $P < 0.1024$ ◦ Average LE reflex score (Mean ± SD) decreased 1.8 points from 2.5 ± 1.2 before treatment to 0.7 ± 1.1 after 12 months post treatment , $P < 0.0001$ • Upper extremities (UE): ◦ After 1 year of continuous ITB, the average UE Ashworth score (Mean ± SD) decreased 1.3 points from 3.0 ± 1.2 before treatment to 1.7 ± 1.0 after 12 months post treatment , $P < 0.0001$ ◦ Average UE spasm score (Mean ± SD) decreased 1.0 points from 1.2 ± 1.6 before treatment to 0.2 ± 0.6 after 12 months post treatment , $P < 0.0135$ ◦ Biceps reflex score (Mean ± SD) decreased 1.8 points from 2.3 ± 0.7 before treatment to 0.5 ± 0.9 after 12 months post treatment , $P < 0.0001$ ◦ No statistically significant change in the muscle tone and spasm frequency at the 6 month follow-up versus 12 month follow-up. • Baclofen dosage: ◦ At the end of 12 months of treatment, the average dosage of ITB to achieve this reduction was 263 ± 91 µg/day (range 160 to 470 µg/day). • Other issues: ◦ One patient after 1 year of treatment became independent with activities of daily livings (ADLs) and transfers and accepted full time employment ◦ One patient achieved independence with feeding and was able to maneuver her power wheelchair independently for the first time ◦ All dependent patient were more comfortable and were easier to manage at home with regard to hygiene, ADLs, and assisted transfers ◦ No patients had changes in urinary voiding patterns ◦ Post operative headaches with nausea in two patients ◦ Two patients developed seizures 1 year after pump placement ◦ Three patients had improvement in their dysarthria ◦ One patient had profound improvement in communication, able to go from part-time employment to full-time employment **Authors conclusion** Continuously infused ITB can reduce spastic hypertonia in the upper extremities and lower extremities associated with long standing cerebral palsy. This reduction in tone will allow more freedom of movement and the potential for improved function.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	25. Becker R, Alberti O, Bauer BL. Continuous intrathecal baclofen infusion in severe spasticity after traumatic or hypoxic brain injury. J Neurol.1997;244:160-166
Study Type / Methods	Pre and post intervention study at the Philipps University Hospital, Baldingerstrasse, Marburg, Germany. The article report on the results in treating 18 patients with severe spasticity following traumatic or hypoxic brain injury. Eighteen patients with severe spasticity from traumatic brain injury or hypoxic brain injury were treated with continuous intrathecal baclofen infusion (CIBI). Muscle tone and spasms were assessed at admission and at discharge according to the Ashworth and Spasm frequency scores. For the assessment, the patient's highest Ashworth score was always noted. In patients 1 and 2 a significant difference in Ashworth scores between the right and left side. In these two patients the mean Ashworth score was calculated for both sides. Additional assessments, for instance of function and pain, were difficult or even impossible in these patients. Pain was assumed when patients made typical, pain associated gestures and facial movements.
LE	II-2
Number of Patients and Patient Characteristics	18 patients • 13 males, 5 females • Mean age 41 years, range (2.5 to 70 years) • 6 patients suffered from severe traumatic brain injury, 3 patients had severe multiple trauma with brain damage resulted from hypoxia, 9 patients had hypoxic brain injury • 1 patient mildly disabled, 5 severely disabled, 12 in vegetative state • 12 patients were bedridden, 6 partially mobile
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Synchromed 8611 H)
Comparison	No comparator
Length of follow up (if applicable)	Ranges from 13 to 54 months
Outcome measures/ Effect size	Changes in baseline (preoperative) and at last follow-up treatment: All patients responded to intrathecal baclofen infusion with a reduction of muscle tone and spasms • Ashworth scale score (Mean): ◦ At last follow-up decreased from preoperative value of 4.5 to a postoperative value of 2.33, where passive movements had been nearly impossible, later showed only a slight increase in tone and could be moved easily • Spasm Frequency Scale (SFS) score (Mean): ◦ The mean Spasm frequency score decreased from preoperative value of 2.16 to postoperative value of 0.94, which means that overall spontaneous full spasms did not appear anymore • Major therapeutic goals, to improve the feasibility of sufficient nursing and physiotherapy and to reduce pain were achieved in all patients: ◦ Transfer to wheelchairs was easier and patients were able to sit in them longer. Of the 12 bedridden patients, at least 8 could be temporarily mobilised in wheelchairs; for 3 patients mobilisation in bed was possible for the first time and only in 1 patient was the situation unchanged. ◦ Of the 6 patients who were already partially mobilised before pump implantation, 3 improved further, in 1 unchanged and in 2, assessment has not yet completed. ◦ In few patients limb contractures limited effective mobilisation to some extent. • Decubitus ulcer: ◦ 11 patients had decubitus ulcer at admission. In 5 the ulcers healed completely and in 5 they improved.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	26. Ochs G, Struppler A, Mehyerson BA, Linderoth B, Gybels J, Gardner BP, Teddy P, Jamous A, Weinmann P. Intrathecal baclofen for long-term treatment of spasticity: Journal of Neurology, Neurosurgery, and Psychiatry. 1989;52:933-939
Study Type / Methods	Pre and post intervention study at four independent hospitals in four European Countries following identical investigational protocols and using the same, programmable drug-administration device (DAD) for intrathecal application of baclofen as treatment of spasticity. Strict records of adverse events, patient related and other pertinent data were collected. Many of the patients were video-recorded before and after treatment. The effect of treatment was quantified by clinical ratings, using the Ashworth-scale for muscle tone assessment and rating rates for frequency and severity of spontaneous spasms and strength of tendon reflexes. Electrophysiological measurements (EMG) recordings of motor responses were performed in a subgroup of patients to quantify the therapeutic outcome.
LE	II-2
Number of Patients and Patient Characteristics	28 patients who suffered from severe chronic para-or tetraspasticity with various aetiologies. • 14 males, 14 females • Mean age 46 (SD=12.2) years, range (24 to 64 years) • Most confined to wheelchair or bedridden, unable to walk and dependent on continuous nursing care • Most suffered from pain due to increased muscle tone or spontaneous spasms
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Synchromed 8611 H)
Comparison	No comparator
Length of follow up (if applicable)	24 months (2 years)
Outcome measures/ Effect size	Changes in baseline (preimplant) and at follow-up treatment: • Ashworth scale score, Mean (SD): ◦ Shortly after the implantation and onset on intrathecal therapy the average muscle tone was reduced from 3.6 (0.35) to 1.75 (0.31). It further decreases to almost normal values in the following months. • Spasm and reflexes: ◦ Spasms were markedly reduced in all cases. ◦ Decreased average number of spasms per hour over time. However, slight increase occurred during the first year. Effects on spasms developed later and with higher baclofen doses as compared with muscle tone. ◦ Decreased hypereflexic activity of the bladder, resulting in less frequent voiding. • Baclofen dosage: ◦ Infusion of 50 to 800 µg/day of baclofen completely abolished spasticity **Authors conclusion** This procedure is recommended for spasticity of spinal origin refractory to physiotherapy and oral medication. It is preferable alternative to ablative surgical intervention.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	27. Azouri P, Mane M, Thiebaut JB, Denys P, Remy-Neris O, Bussel B. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. Arch Phys Med Rehabil. 1996;77:35-39
Study Type / Methods	Pre and post intervention study at a neurological rehabilitation department of a university hospital in France. The aim of the study was to assess long-term efficacy and functional benefits of intrathecal baclofen for severe spinal spasticity. Eighteen patients with severe and disabling spinal spasticity received intrathecal baclofen by an implantable pump. Patients' evaluation were done before implantation and during follow-up by spasticity measures (Ashworth scale, spasms frequency score), and by the Functional Independence Measure (FIM) - French adaptation by P. Minaire. FIM consists of 18 items divided into 6 categories including self-care, sphincter control, mobility, locomotion, communication, and social cognition. These items are grouped into 2 fundamental subsets, one measuring motor and the second cognitive functions. Scoring on each item is based on a 7-point scale, ranging from complete independence Value = 7) to complete dependence (total assistance required = 1).
LE	II-2
Number of Patients and Patient Characteristics	18 patients who suffered from severe chronic para-or tetraspasticity with various aetiologies. • 14 males, 4 females • Average age was 38.5 years (SD = 11.6) • Average duration of disease was 8.7 years (SD = 8.7), but highly variable according to the pathology (19.5 years for multiple sclerosis (MS) patients, 5.7 for other cases) Inclusion criteria: • Severe disabling spinal spasticity (Ashworth scale score ≥ 4, spasm frequency score ≥ 3) • Ineffectiveness of oral antispastic drugs • Positive response to intrathecal baclofen
Intervention	Continuous ITB infusion Programmable pump device
Comparison	No comparator
Length of follow up (if applicable)	Average follow-up was 37.4 months (range; 9 to 72 months) 10 patients were treated for more than 30 months, and 4 more than 5 years
Outcome measures/ Effect size	Changes in baseline (preimplant) and at follow-up treatment: • Spasticity control: ◦ 1 patient died after 12 months because of severe swallowing disorders related to MS ◦ In one case treatment was interrupted after 9 months because of severe side-effects ◦ In all cases, an improvement of at least 2 points on both Ashworth and spasms scale scores could be maintained through follow-up ◦ The difference between baseline and 6-month spasticity scores was statistically significant (paired comparison by Wilcoxon signed rank test: Z = - 3.79, P < 0.001 for Ashworth score, and Z = 3.78, P < 0.001, for spasms scale score) • Functional improvement, (Mean ± SD): ◦ The average motor FIM score for 18 patients was 39.9 ± 18.1 before treatment, and 58.5 ± 28.7 at 6 months (Wilcoxon Z = - 3.62, P < 0.001). Improvement was statistically significant for all individual items, except for eating (most patients independent), and stair climbing (that was possible for only 2 patients). ◦ No modification was for cognitive subscore (scores remained at 7 for every item for all patients). ◦ Type and amount of improvement were however very different according to the nature and level of spinal cord lesion. Most dramatic improvements were observed in the 12 patients exhibiting a thoracic or low cervical lesion (average motor FIM score evolving from 50.9 ± 9.7 to 76.3 ± 15.5, Z = - 3.06, P < 0.01). Functional benefits were particularly marked for the following items, which gained 2 or more FIM scores in average: bathing, dressing lower body, and the 3 items related to transfers. In 7 of these 12 patients, locomotion also improved. In 5 patients, walking ability improved (average initial FIM walking score: 3.6 ± 0.87, and 6-month score: 5.8 ± 0.2), and 2 of these patients acquired the ability to climb stairs. ◦ Functional improvement for the 6 most severely disabled patients, who were nearly totally dependent, was less obvious but still significant (average motor FIM score initially: 18 ± 6.6, at 6-month follow-up: 22.8 ± 6.7, Z = - 2.03, P < 0.05). ◦ In cases of severe upper limb dysfunction, FIM was only improved for wheelchair displacements, due to better sitting position, but nursing became easier and life comfort was enhanced. • Baclofen dosage: ◦ Average initial dose of intrathecal baclofen after pump implantation was 142.8 ± 90.9 µg (range; 20 to 425 µg). Average dosage at 6 months after implantation was 312.1 ± 189.9 µg. Mean dosage increased from 6 to 12 months and no dosage increased was observed after 12 months. **Authors conclusion** Efficacy remained stable after 6 to 9 months. Marked improvement of functional independence was observed in paraplegic patients. Improvement was less spectacular in patients with severe upper limb dysfunction, but nevertheless appreciable in terms of life comfort and use of attendants.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	28. McClelland S, Bethoux FA, Boulis NM, Sutliff MH, Stough DK, Schwetz KM, Gool DA, Harrison M, Pioro EP. Intrathecal baclofen for spasticity-related pain in amyotrophic lateral sclerosis: efficacy and factors associated with pain relief. Muscle Nerve. 2008;37:396-398
Study Type / Methods	Pre and post intervention study conducted in the USA. The aim of the study was to define the impact of implantable intrathecal baclofen (ITB) on pain relief in a cohort of amyotrophic lateral sclerosis (ALS) patients. From 2003 to 2005, eight patients with ALS received ITB for pain associated with intractable spasticity. Following successful test injection, patients were referred to the Cleveland Clinic Foundation for programmable intrathecal infusion system implantation. Pain was quantified by patient response to a physical therapist using a 0 to 10 scale, with 0 representing no pain and 10 representing maximal pain. Complete pain relief was defined as a zero on the pain scale. The mean modified preoperative pain score was 7.69, ranging from 6 to 10. The mean pre-operative Ashworth score was 2.93. Patient who do not receive adequate relief of spasticity following test injection did not undergo pump implantation. Post operative pain relief was quantified with the same 0 to 10 scoring system used preoperatively.
LE	II-2
Number of Patients and Patient Characteristics	8 patients who suffered from ALS with intractable spasticity and related pain • 5 men, 3 women • Mean age at survey was 43.8 years • Age range (33 to 77 years) • ALS symptom duration ranged from 14 to 108 months, with an average of 47.4 months at surgery
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up was 9.8 months.
Outcome measures/ Effect size	Changes in preoperative and postoperative: • Pain score: ◦ Following ITB pump placement, the average pain score was 3.56 (range; 0 to 8), a statistically significant reduction of 54% from preoperative scores, P = 0.0082 ◦ Six patients (75%) experienced reduction of preoperative pain scores, three of whom had complete pain relief (postoperative pain score of 0) ◦ The degree of pain score reduction following preoperative ITB test injection was predictive of the degree of postoperative pain reduction following ITB implantation in six of the seven patients with recorded preoperative ITB test injection results • Ashworth score: ◦ Mean postoperative Ashworth score was 1.72 (reduced compared with preoperative, 2.93) **Authors conclusion** These result support ITB as a treatment modality for pain associated with spasticity in ALS.
General comments	Retrospective

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	29. Schiess MC, Oh IJ, Stimming EF, Lucke J, Acosta F, Fisher S, Simpson RK. Prospective 12-month study of intrathecal baclofen therapy for poststroke spastic upper and lower extremity motor control and functional improvement. Neuromodulation. 2011;14: 38-45
Study Type / Methods	Prospective pre and post intervention study conducted at Houston, Texas, USA. The aim of the study was to assess the effects of intrathecal baclofen (ITB) therapy for treatment of poststroke hemiparesis on quality of life, functional independence, and upper and lower extremity (UE, LE) motor functions. Prospective observational study of adult men and women with a minimum 6-month stroke related spastic hemiparesis graded ≥ 2 in UE and LE on Modified Ashworth Scale (MAS). Patients served as their own control with measures compared with pre-implant with 12 months post ITB including: MAS, manual muscle test (MMT), gait distance / velocity, Functional Independence Measures (FIM), stroke-specific quality of life scale (SSQL), and upper extremity manual activity log.
LE	II-2
Number of Patients and Patient Characteristics	30 patients • 17 males, 13 females • Mean age ± SD (52 ± 12 years) • Age range (27 to 75 years) • Left sided hemiparesis, n=19 (73%) • Stroke classification: ◦ Ischaemic ◦ Intracranial haemorrhage • Poststroke interval, years (Mean ± SD): ◦ 6.4 ± 9 years • Functional status: ◦ Employed; 7(27%) ◦ Disabled; 15 (58%) ◦ Retired; 4 (15%) Inclusion criteria: • Men and women aged 18 to 75 years • Minimum post stroke duration of 6 months • Failure of oral antispasmodic therapy • MAS score of ≥ 2 in affected limbs • Positive response to ITB trial
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Changes in pre-implant and 12 months post ITB therapy (N = 26, Mean ± SD):** 4 discontinued after 6 month follow-up: 2 device explanted, due to aesthetic concerns (N=1), discomfort (N=1). 2 lost to follow-up, critically ill (N=1), moved out of state (N=1) • Spastic tone and motor strength lower extremity (LE): ◦ Spastic tone in the LE at pre-implant, MAS = 2.21 ± 0.76, was reduced significantly when compared at 12 months post ITB therapy, MAS = 1.51 ± 0.66, P ≤ 0.001 ◦ Strength in the LE at pre-implant, MMT = 1.78 ± 0.92, was increased significantly when compared at 12 months post ITB therapy, MAS = 2.95 ± 1.55, P ≤ 0.0001 • Spastic tone and motor strength upper extremity (UE): ◦ Spastic tone in the UE at pre-implant, MAS = 2.4 ± 0.6, was reduced significantly when compared at 12 months post ITB therapy, MAS = 1.8 ± 0.05, P ≤ 0.01 ◦ Strength in the UE at pre-implant, MMT = 1.7 ± 1.1, was increased significantly when compared at 12 months post ITB therapy, MAS = 2.6 ± 1.2, P ≤ 0.05 • Functional independence (FIM scores): ◦ At pre-implant activity, the mean functional status for each measure fell between minimal assistance (4) and modified independence (6) on the (1 to 7) FIM scale. All FIM activities improved significantly after 12 months post ITB therapy (P < 0.05), except for bed mobility and dressing of the lower body • Gait distance and velocity (N=23): ◦ Gait performance improved after 12 months of ITB therapy when compared with baseline performance. ◦ Velocity at pre-implant 0.55 ± 0.26 m/sec, compared with 0.77 ± 0.36 m/sec at 12 months post ITB, P ≤ 0.05 ◦ 6-minute walk distance pre-implant of 558 ± 254 ft, compared with 746 ± 368 ft at 12 months post ITB, P ≤ 0.05 • Stroke-specific quality of life scale (SSQL), N=26: ◦ SSQL showed significant improvement comparing the baseline pre-implant values with values at 12 months post ITB specifically for the domains of family roles, mobility, personality, self-care, social roles, thinking UE function, and work/productivity, P < 0.05 ◦ No significant change in the domains of language, energy, mood, and vision • Upper extremity function: ◦ Intrathecal baclofen therapy for 12 months significantly increased the amount of use (AOU) and quality of movement (QOM) of the affected UE in performing a common activities of daily living P < 0.0001) ◦ AOU was positively correlated with the QOM, r = 0.98, meaning the more the arm was used performing the 30 total fine and gross motor activities, the more the QOM improved **Authors conclusion** Regardless of duration of spastic hemiparesis, a reduction in tone with ITB therapy facilitates motor strength improvement and is associated with clinically significant improvements in functional independence and quality of life.
General comments	Industry sponsored Assessor blinded to antispasmodic drug regimen at pre-implant baseline or the ITB baclofen dosing

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	30. Ivanhoe CB, Francisco GE, McGuire JR, Subramaniam T, Grissom SP. Intrathecal baclofen management of poststroke spastic hypertonia: implications for function and quality of life. Arch Phys Med Rehabil. 2006;87:1509-1515
Study Type / Methods	Prospective open label multicentre consisting of 2 trial (pre and post intervention study) at 24 stroke treatment centres in the USA. The aim of the study was to evaluate the impact of intrathecal baclofen (ITB) on function and quality of life (QOL) and to obtain efficacy and safety data in poststroke spastic hypertonia. The study consists of 2 phases. Phase I was a bolus screening trial of ITB. A positive response, defined as a mean drop of 1 point on the Ashworth scale in the affected upper and lower limbs, was prerequisite to phase II, which involved implantation of the ITB pump. Participants were recruited in a consecutive manner across 24 treatment centres in the United states. Participants included men and women between 16 to 80 years of age who were at least 6 months poststroke and diagnosed with spastic hypertonia in at least 2 limbs (score $\geq$ 3 on Ashworth scale). Participants were evaluated before ITB therapy (baseline) during screening, at 3 and 12 months post ITB implant. Main outcome measures include FIM and QOL [Sickness Impact Profile (SIP) changes, Ashworth scale, and safety. SIP is a valid and reliable, frequently used health-related QOL measure, which has 2 domains: psychosocial and physical These domains are further divided into 12 categories (body care and movement, mobility, ambulation, emotional behaviour, social interest, alertness behaviour, communication, sleep and rest, home management, work, recreation and pastimes, eating) that reflect specific behaviour. The individual items were weighted with a maximum total score of 100. Negative numerical changes indicate perceived improvement in QOL.
LE	II-2
Number of Patients and Patient Characteristics	94 participants, 74 implanted with device • 52.1% males, 47.9% females • Mean age at enrolment was 57.2 ± 13.0 years (range, 23.7 to 81.9 years) • Time from stroke to enrolment was 3.3 years ± 3.8 years (range; to 25.2 years)
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in, pre-implant and 12 months post ITB therapy [N=74 (intention to treat analyses), Mean ± SD): • 17 participants did not complete the 12 month follow-up for the following reasons: ◦ 3 lost to follow-up, 6 requested withdrawal, 3 deaths, 5 had their device explanted during the course of the study because of 1 hardware failure, 1 infection, 1 chest wall pain, and 2 with lack of expected improvement • Functional independence (FIM scores): ◦ Overall, mean total FIM scores improved significantly, P = 0.005 ◦ Mean total FIM scores increased 3.00 ± 7.69 (P = 0.001) from baseline to 3 months and 2.86 ± 10.13 (P = 0.017) from baseline to 12 months • Quality of Life (SIP scores): ◦ Overall, mean total SIP scores improved significantly, P < 0.001 ◦ Total SIP scores improved - 3.24 ± 9.10 (P = 0.003) from baseline to 3 months and - 4.32 ± 8.73 (P < 0.01) from baseline to 12 months ◦ SIP scores improved significantly in both physical and psychosocial domains (P < 0.001). As compared with baseline, at 3 months, the physical and psychosocial domains improved - 2.24 ± 9.89 (P = 0.55) and - 4.51 ± 12.30, (P = 0.002), whereas at 12 months improvements were seen of - 4.55 ± 10.65 (P < 0.001) and - 4.91 ± 11.62, (P < 0.001), respectively. • Efficacy (Ashworth scale scores): ◦ Combined average Ashworth scale score of the upper and lower limbs decreased significantly (P < 0.001) overall, and by 1.27 ± 0.76 (P < 0.001) at 3 months and 1.39 ± 0.73 (P < 0.001) at 12 months from baseline ◦ Overall, a significant decrease in Ashworth scale score of the affected side of 0.97 ± 0.87 (P < 0.001) at 3 months and 1.11 ± 0.90 (P < 0.001) at 12 months was observed for upper extremities ◦ Overall, a significant decrease in Ashworth scale score of the affected side of 1.44 ± 0.91 (P < 0.001) at 3 months and 1.52 ± 0.96 (P < 0.001) at 12 months was observed for lower extremities • Muscle strength of limbs unaffected by stroke: ◦ Overall changes in manual muscle test (MMT) scores were not significant (P = 0.321) ◦ Changes relative to baseline were also not significant at 3 months (0.04 ± 0.54 (P = 0.553) and 12 months (- 0.07 ± 0.87 (P = 0.462) **Authors conclusion** There was significant improvement in function, QOL, and spastic hypertonia at 3 and 12 months after implant, without adversely affecting muscle strength of the unaffected limbs, Data suggest that ITB is a safe and efficacious treatment for spastic hypertonia resulting from stroke.
General comments	Industry sponsored

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	31. Francisco GE, Boake C. Improvement in Walking Speed in poststroke spastic hemiplegia after intrathecal baclofen therapy: A preliminary study. Arch Phys Med Rehabil. 2003;84:1194-1198
Study Type / Methods	Pre and post intervention study at a tertiary care centre, Houston, Texas, USA. The aim of the study was to explore whether intrathecal baclofen (ITB) therapy improves ambulation in stroke survivors. Participants were from the spastic hypertonia clinic of a freestanding rehabilitation hospital over a period from late 1998 to 2001. Participants underwent a screening procedure to determine responsiveness to ITB. The ITB pump for continuous infusion was implanted with the patient under general anaesthesia. The 4 outcome measures were assessed before and after pump implantation. The 4 outcome measures include customary walking speed which was calculated for the time it took a participant to walk 50 ft (15 m), with or without assistance, on a level surface at a self-comfortable pace, functional walking category, Modified Ashworth scale and Functional Mobility Score. Five items were rated to reflect functional mobility skills; locomotion-walking and stairs item of FIM instrument, the community access item of the FAM, and 2 unpublished items (Sit - stand, Stand - Sit).
LE	II-2
Number of Patients and Patient Characteristics	10 adults with poststroke hemiparesis who were ambulatory at the time of pump implantation. • 5 males, 5 females • Mean age was 51.7 years • Mean time interval from stroke onset to pump implantation was 28.6 months (median ± SD, 24 ± 15.8 months; range; 9 to 55 months) Inclusion criteria: • Spasticity resulting from stroke • MAS score ≥ 2 in at least 2 limbs • Age ≥ 18 years • Inadequate spasticity control with other pharmacologic and physical modalities • No known allergy to baclofen • Ambulatory at any level of assistance before pump implantation
Intervention	Continuous ITB infusion Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean time interval from pump implantation to follow-up 8.9 months (median, 7 ± 6.1 months; range, 4 to 25 months)
Outcome measures/ Effect size	Outcome Measures at baseline and postimplantation follow-up (Mean ± SD) • Walking speed: ◦ Walking speed increased by at least 1 cm/s in 9 of 10 participants ◦ Mean improvement in walking speed from baseline to postimplantation was 15.4 ± 14.4 cm/s (range; 0.6 to 50.1 cm/s), P = 0.051. Mean walking speed increased to 52.0 ± 37.6 cm/s at follow-up from 36.6 ± 29.4 cm/s, at baseline. ◦ Effect size of the change in walking speed was 1.07, which is a large effect size • Functional mobility: ◦ Functional mobility score improved in 6 of 10 participants, with the mean increase being 2.7 ± 2.9 points (range; 0 to 7), P = 0.0277 ◦ Effect size of the improvement score was 0.93, which is a large effect size • Modified Ashworth scale (MAS) score: ◦ Mean lower-extremity MAS score decreased in all 10 participants ◦ Mean reduction being 1.6 ± 0.5 points (range; 0.9 to 2.3), P = 0.0051 ◦ Effect size of spasticity reduction was 3.2 which is a large effect size • Functional walking category: ◦ 3 participants improved their functional walking category **Authors conclusion** This preliminary study suggests that ITB therapy, in combination with physical therapy, may improve walking speed and functional mobility in ambulatory individuals with poststroke spastic hemiplegia.
General comments	Industry sponsored

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	32. Mota F, Stignani C, Antonello CE. Upper limb function after intrathecal baclofen treatment in children with cerebral palsy. J Padiatr Orthp. 2008;28(1):91-96
Study Type / Methods	Pre and post intervention study at the Paediatric Orthopaedics Department of "V. Buzzi" Children's Hospital, Milan, Italy. The aim of the study was to evaluate the motor function of the upper limbs in patients with cerebral palsy (CP) treated with ITB. A consecutive series of 20 patients with spastic CP, aged between 5 and 15 years and able to understand the required tasks from the Melbourne scale implanted with pumps was studied. The patients were followed up over 12 month period for assessment of the upper limb function with the Melbourne Assessment of Unilateral Upper Limb Function scale, an assessment protocol that measures the quality of upper limb function in children between the ages 5 and 16 years with neurological impairment. The tool is composed of 16 items with a maximum score of 122. The patient performance is video recorded and to assign a score after the test is completed. At every follow-up, the patients were also administered a subjective questionnaire for internal use that investigated the aspects of patient's life through 26 questions. Degree of satisfaction with the treatment was investigated through 2 questions.
LE	II-2
Number of Patients and Patient Characteristics	20 patients • 15 boys, 5 girls • Average age at the time of implantation was 11.4 years (SD, 3.57 years, range 5 to 15 years • 9 patients had spastic diplegia, 11 had quadriplegia • All 20 patients were classified between levels II and V of the Gross Motor Function Classification System (GMFCS) • 2 patients GMFCS level II, 8 patients GMFCS level III, 7 level IV, 3 level V
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in pre-ITB and 12 months post ITB (N = 20) • Upper Limb Ashworth scale score: ◦ Upper limb average Ashworth score decreased from 3.4 (SD, 0.68) to 1.7 (SD, 0.66), $P < 0.05$ • Melbourne Assessment percentage total score of dominant upper limb: ◦ Total average score for the dominant limb increased from a percentage value of 73.16% (SD, 14.4%) to a value at 12 months of 81.56 (SD, 12.34%) ◦ 5 patients showed a score variation greater or equal to 12% (clinically significant) • Melbourne Assessment percentage total score of non dominant upper limb: ◦ Total average score for the non dominant limb increased from a percentage value of 63.44% (SD, 22.5%) to a value at 12 months of 70.20% (SD, 21.59%) ◦ 3 patients showed a score variation greater or equal to 12% (clinically significant) • Melbourne Assessment percentage total score: ◦ An analysis of total pre treatment and post treatment scores for range of movement, target accuracy, and fluency subskills showed statistically significant improvements ($P < 0.05$) ◦ 25% of study population showed an improvement in quality of function of at least 1 limb ◦ In both the dominant and non dominant limb, there were 9 items (56%) with statistically significant variations • Subjective questionnaire: ◦ 17 patients (85%) reported a better use and improved ability in the upper limb, whereas no changes were found in 3 patients (15%) ◦ Reduced rigidity was reported in all 20 patients and 18 of them also experienced improvements during the rehabilitation sessions ◦ Improvements were also reported in the management of daily activities. Level of independence was reported as improved in 90% of the cases ◦ 18 patients (90%) expressed satisfaction with the procedure, and most patients (18 of 20) would do it again. **Authors conclusion** The subjects with CP of different degrees of severity had an improvement in quality of the upper limb function and showed overall satisfaction with the results achieved. The study also shows the importance of evaluating the quality of upper limb function in children with CP treated with ITB therapy.
General comments	

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Bibliographic Citation	33. Albright AL, Barry MJ, Pat Fasick M, Janosky J. Effects of continuous intrathecal baclofen infusion and selective posterior rhizotomy on upper extremity spasticity. Paediatr Neurosurg.1995;23:82-85
Study Type / Methods	Comparative study at the Children's Hospital of Pittsburgh. The aim of the study was to compare the effects of continuous intrathecal baclofen infusion (CIBI) and selective posterior rhizotomy (SPR) on upper extremity (UE) spasticity and range of motion in children with cerebral palsy. Spasticity was assessed with the Ashworth scale of muscle tone and range of motion was evaluated. The charts of the first 38 patients with cerebral spasticity who had been treated with CIBI for at least 6 months were matched with 38 patients who had been treated with SPR during the past 8 years. Patients were matched according to pre treatment UE muscle tone and functional status. The CIBI dosage had been titrated to reduce lower extremity spasticity and improve lower extremity function, rather than to improve UE tone. The pre treatment muscle tone in the two groups was virtually identical. Function was also matched according to level of functional ability, as either non functional if they were incapable of independent self-care, and as functional, if they were capable of self care.
LE	II-2
Number of Patients and Patient Characteristics	• 38 patients with cerebral spasticity in CIBI group ◦ Baseline UE Ashworth score prior to treatment was 2.07 ± 0.82 • 38 patients with cerebral spasticity in SPR group ◦ Baseline UE Ashworth score prior to treatment was 2.03 ± 0.74
Intervention	Continuous ITB infusion Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	Selective Posterior Rhizotomy (SPR)
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Changes in upper extremity Ashworth score pre treatment and post treatment for CIBI and SPR: • Upper extremity (UE) Ashworth scale score for patients treated with CIBI: ◦ Mean upper extremity Ashworth score declined from 2.07 to 1.84 at 6 months, and to 1.66 after 1 year ($P < 0.001$) • Upper extremity (UE) Ashworth scale score for patients treated with SPR: ◦ Mean upper extremity Ashworth score declined from 2.03 to 1.78 at 6 months, and to 1.7 after 1 year ($P < 0.005$) ◦ Likelihood of clinically significant reduction in muscle tone (one point or greater) was greater in children with a higher pre treatment UE muscle tone ◦ No correlation between the percentage of posterior lumbar roots divided in SPR and the subsequent reduction in UE tone • No significant changes in the range of motion in any UE joint at either 6 or 12 months, after either CIBI or SPR **Authors conclusion** Both CIBI and SPR significantly reduce UE spasticity, in addition to the previously documented reduction in lower extremity spasticity.
General comments	

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Bibliographic Citation	34. Burns AS, Meythaler JM. Intrathecal baclofen in tetraplegia of spinal origin: efficacy for upper extremity hypertonia. Spinal Cord. 2001;39:413-419
Study Type / Methods	Pre and post intervention study at the University of Alabama at Birmingham, Alabama, USA. The aim of the study was to evaluate the efficacy of intrathecal baclofen (ITB) for upper extremity spastic hypertonia in tetraplegia of spinal origin. The medical records of 14 individuals with tetraplegia of spinal origin who underwent intrathecal baclofen pump placement were reviewed. The effects of intrathecal baclofen on spasm frequency, deep tendon reflexes, and tone (Ashworth scale) were assessed for the upper and lower extremities for a 1 year follow-up period.
LE	II-2
Number of Patients and Patient Characteristics	14 patients with spinal cord pathology afflicting the cervical segments (C1 – T1) • All study subjects had sustained their injuries at least 6 months prior to baclofen pump placement and failed to response to oral agents • 12 males, 2 females • Age range (25 to 64 years)
Intervention	Continuous ITB infusion Programmable pump device
Comparison	No comparator
Length of follow up (if applicable)	12 months (1 year)
Outcome measures/ Effect size	**Changes in pre-ITB and 12 months post ITB** Lower extremities • Ashworth scale score (Mean ± SD): ◦ Average Ashworth score (tone) decreased from 3.1 ± 1.3 at baseline to 1.7 ± 0.9 at 12 months (P < 0.0001) • Spasm score (Mean ± SD): ◦ Average spasm score decreased from 3.3 ± 0.9 at baseline to 1.8 ± 1.5 at 12 months (P = 0.0011) • Reflexes (Mean ± SD): ◦ Average baseline reflex score was 2.8 ± 1.3 at baseline compared to 0.4 ± 0.9 at 12 months (P < 0.0001) Upper extremities • Ashworth scale score (Mean ± SD): ◦ Average Ashworth score (tone) decreased from 2.4 ± 1.1 at baseline to 1.8 ± 1.0 at 12 months (P < 0.0001) • Spasm score (Mean ± SD): ◦ Average spasm score decreased from 2.3 ± 1.6 at baseline to 0.5 ± 0.9 at 12 months (P = 0.2503) • Reflexes (Mean ± SD): ◦ Average baseline reflex score was 2.3 ± 0.2 at baseline compared to 0.9 ± 0.2 at 12 months (P < 0.0001) • Dosage ◦ Average initial dose requirements were 120 µg/day ± 22.1 compared to 299.0 µg/day ± 183.0 at 12 months, P < 0.0001 **Authors conclusion** ITB is a safe and effective intervention in treating upper extremity hypertonia of spinal origin.
General comments	Retrospective

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	35. Gianino JM, York MM, Paice JA, Sbott P. Quality of life: Effect of reduced spasticity from intrathecal baclofen. Journal of Neuroscience Nursing. 1998;30 (1):47-54
Study Type / Methods	Pre and post intervention study conducted in Chicago, Illinois, USA. The aim of the study was to explore the effect of reduced spasticity on quality of life using intrathecal baclofen therapy. A prospective study using a one-group, pretest-postest design was implemented. The sample was a convenience sample which included 25 subjects diagnosed with intractable spasticity of spinal origin who met the criteria for treatment with intrathecal baclofen. The patients were implanted with a SynchroMed drug pump (Minneapolis, MN) to administer intrathecal baclofen continuously. Subjects were given the Ferrans and Powers Quality of Life Index (QLI) and Sickness Impact profile (SIP) prior to receiving intrathecal baclofen as well as at three month intervals ending at 12 months after beginning the therapy. The Ferrans and Powers QLI is a 72 item tool that has four subscales: health & functioning, socioeconomic, physiological / spiritual and family. The SIP has two subscales: physical subscore and psychological.
LE	II-2
Number of Patients and Patient Characteristics	21 subjects diagnosed with intractable spasticity of spinal origin • 60% females, 40% males • 80% Caucasian, 16% African-American, 4% Hispanic • Mean age was 39.4 years (SD = 11.2; range 21 to 70 years) • 68% not employed, 12% worked part time, 16% work full time • Subjects had experienced spasticity for an average of 42.0 months (SD = 47.0; range 4 to 216 months)
Intervention	Continuous ITB infusion Programmable pump device (SynchroMed drug pump (Minneapolis, MN)
Comparison	No comparator
Length of follow up (if applicable)	12 months (1 year)
Outcome measures/ Effect size	**Changes in pre-ITB and 12 months post ITB** • Ashworth scale score (Mean ± SD): ◦ Mean Ashworth score decreased significantly from 3.78 ± 0.82 at baseline to 1.48 after one year, (Friedman test; P = 0.00000014) • Spasm score (Mean ± SD): ◦ Mean spasm score decreased significantly from 2.6 ± 1.2 at baseline to 0.5 ± 0.8 after one year, (Friedman test; P = 0.000017) **Quality of Life** • Ferrans and Powers quality of Life Index: ◦ None of the changes in Ferrans and Powers QLI total or subscale scores for the different time points were statistically significant • Sickness Impact Profile (SIP): ◦ Statistically significant difference between the baseline and 12 month SIP total score; 29.7 at baseline reduced to 21.2 at 12 months, P = 0.0042. ◦ 13 of 16 patients with complete data demonstrated improved physical subscale scores at 12 months, compared to baseline and 3 showed decline (P = 0.0213) ◦ 12 patients had improved psychological subscores at 12 months, compared to baseline, and 3 showed decline (P = 0.0352) ◦ A qualitative analysis of 2 open ended questions revealed positive statements about the change in quality of life when spasticity is well-controlled.
General comments	

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Bibliographic Citation	36. Zahavi A, Geertzen JBH, Middel B, Staal M, Rietman JS. Long term effect (more than five years) of intrathecal baclofen on impairment, disability, and quality of life in patients with severe spasticity of spinal origin. J Neurol Neurosurg Psychiatry. 2004;75:1553-1557
Study Type / Methods	Pre and post intervention study at nine Dutch Hospitals The aim of the study was to evaluate long term change in impairment, disability, and health related functional status in patients with severe spasticity who received intrathecal baclofen. A long term (more than five years) observational longitudinal follow-up study assessing 21 patients who received intrathecal baclofen given by a programmable pump. Patients had chronic disabling spasticity which did not respond to oral antispasmolytic agents. Clinical efficacy was assessed by Ashworth scale and spasm score; disability by expanded disability status scale (EDSS), ambulation index (AI), and incapacity status scale (ISS); and health related quality of life by the sickness impact profile (SIP) and the Hopkins symptom checklist (HSCL). Non-standardised questionnaire subjectively evaluating the patient's response to treatment of baclofen. The aim is to determine the patients overall satisfaction with treatment, independent of the information obtained from the various clinical and health related measurements.
LE	II-2
Number of Patients and Patient Characteristics	21 subjects diagnosed with intractable spasticity of spinal origin • 12 Males, 9 Females • Mean age (SD) = 54.6 years (12.5 years), range; 31 to 76 years • 11 (53%) had progressive disease, 9 (47%) non progressive disease Inclusion criteria: • Age 18 years or over • Insufficient response to treatment with maximal doses of oral baclofen, dantrolene, and tizanidine • Sufficient understanding of the consequences of the treatment
Intervention	Continuous ITB infusion Programmable pump (SynchroMed drug pump (Minneapolis, MN)
Comparison	No comparator
Length of follow up (if applicable)	Mean duration of treatment was 84.9 months (range 66 to 108 months)
Outcome measures/ Effect size	**Changes in pre-ITB and post ITB (baseline, 26 weeks and final assessment)** **Clinical efficacy** Compared to pre treatment values, there was significant improvement in clinical efficacy: • Spasm score, Mean (SD): ◦ Baseline, 1.79 (0.56), 26 weeks, 0.94 (0.53), final assessment, 0.67 (1.10), final versus baseline, P = 0.001, final versus 26 weeks, P = 0.26 • Ashworth scale score, Mean (SD): ◦ Baseline, 2.82 (0.86), 26 weeks, 1.16 (0.99), final assessment, 0.9 (0.90), final versus baseline, P = 0.00, final versus 26 weeks, P = 0.95 **Disability** A small but significant worsening in the level of disability (EDSS, AI and ISS) • Expanded disability status scale (EDSS), Mean (SD): ◦ Baseline, 7.71 (0.81), 26 weeks, 7.59 (0.86), final assessment, 7.88 (0.91), final versus baseline, P = 0.023, final versus 26 weeks, P = 0.031 • Ambulation Index (AI), Mean (SD): ◦ Baseline, 7.74 (1.48), 26 weeks, 7.64 (1.75), final assessment, 8.05 (1.56), final versus baseline, P = 0.027, final versus 26 weeks, P = 0.125 • Incapacity status scale (ISS), Mean (SD): ◦ Baseline, 25.74 (8.43), 26 weeks, 25.27 (10.38), final assessment, 28.76 (10.36), final versus baseline, P = 0.011, final versus 26 weeks, P = 0.016 ◦ Perceived health status: Sickness impact profile (SIP) and Hopkins symptom checklist (HSCL) ◦ No significant differences with the exception for psychosocial dimension of SIP. • Sickness Impact Profile, Psychosocial dimension, Mean (SD): ◦ Baseline, 13.50 (10.39), 26 weeks, 10.88 (10.90), final assessment, 19.00 (16.91), final versus baseline, P = 0.18, final versus 26 weeks, P = 0.01 • Patients satisfaction: ◦ All patients except two (1 had catheter dysfunction, 1 allergy) were satisfied with the overall treatment and indicated that they would recommend the treatment to other patient with spasticity ◦ The most prominent improvements reported by the patients were increased ease of transfer, better seating posture, ease of care in activities of daily living (passive), and decrease in pain. However, only few patients said that they could carry out more activities than before. **Authors conclusion** Long term administration of intrathecal baclofen delivered by an implanted programmable pump resulted in improved clinical efficacy but not in improvement in disability or perceived health status.
General comments	

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Bibliographic Citation	37. Brochard S, Remy-Neris O, Filipetti P, Bussel B. Intrathecal baclofen infusion for ambulant children with cerebral palsy. Pediatr Neurol. 2009;40: 265-270
Study Type / Methods	Pre and post intervention study conducted at six rehabilitation departments in France. The aim of the study was to assess the effects of continuous intrathecal infusion of baclofen on the gait of ambulant children with cerebral palsy. The study involved a retrospective, consecutive case series of children and young adults who had received intrathecal baclofen infusions. Data were collected for each participant at the time of intrathecal baclofen pump implantation and during the last follow-up visit when a change in dose delivery was effected. Details collected included Gillette Functional Assessment Questionnaire score, use of walking aids, Ashworth Scale score, and joint angle at which the stretch reflex was triggered.
LE	II-2
Number of Patients and Patient Characteristics	21 ambulant children and young adults with cerebral palsy • 12 diplegic children, 8 quadriplegic children, 1 triplegic child • 14 girls, 7 boys • Mean age of 11 years and 10 months (SD, 4 years and 10 months; range, 6 to 22 months) • Gross Motor Function Classification – 17 as level III, 4 as level II • Median initial Gillette Functional Assessment Questionnaire score was 5 (SD,2: range, 2 to 9) • Most of the children had a crouch gait pattern (n = 10) or true equines (n = 8) Inclusion criteria: • Primary diagnosis of cerebral palsy • Able to walk with or without an assistive device at least in physiotherapy
Intervention	Continuous ITB infusion Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean duration of treatment was 25.8 months (range, 5 to 57 months)
Outcome measures/ Effect size	Changes in pre ITB and after ITB treatment (mean of 11.8 months after treatment) • Spasticity Assessment: ◦ Mean Ashworth score reduced after intrathecal baclofen infusion by 1.4 points (SD, 0.52), P < 0.001 • Gait Assessment: ◦ The Gillette Functional Assessment Questionnaire score improved significantly, from 5.04 (SD, 2.1) to 6.10 (SD, 2.1), P = 0.0054 ◦ The scores of 3 children increased by 4 or 5 levels and the scores of 9 children increased by 1 or 2 levels, one child score decreased by 1 or 2 levels • Postural control: ◦ None of the 4 children who did not use a walking aid before intrathecal baclofen infusion required one after treatment ◦ 7 of 17 children using a walking aid before pump implantation improved their postural control, i.e., they use a less supportive walking aid ◦ 4 abandoned their walkers: 2 for tripod crutches, 1 for two crutches, and 1 no longer used walking aid ◦ After treatment, none of the children required walking aids that provided more support than those they previously used **Authors conclusion** Continuous intrathecal baclofen appears to decrease spasticity and improved the gait capacity of children with cerebral palsy.
General comments	Retrospective

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	38. Sadiq AS, Wang GC. Long-term intrathecal baclofen therapy in ambulatory patients with spasticity. J Neurol. 2006;253:563-569
Study Type / Methods	Pre and post intervention study at MS Research and Treatment Centre of New York, Albert Einstein College of Medicine, New York, USA. The aim of the study was to determine the effects of ITB on ambulatory patients with spasticity with particular attention to functional outcomes and ambulation. Patients considered for ITB therapy included those with: 1) moderate to severe spasticity with Ashworth score of ≥ 3 in the most severely affected muscle, 2) intolerance or sub-optimal response to oral anti-spastic agents, 3) relatively intact muscle strength, 4) stable or optimally managed underlying neurological disease. Thirty six patients with severe spasticity previously screened for response to ITB were implanted with programmable pumps that allowed for continuous infusion of ITB. Patients were followed after implantation from 1 to 13 years. Quality of Life (QOL) measure for ambulatory function: All patients self-reported on a modified version of the 12-Item MS walking Scale (MSWS-120. The patients recorded their responses on a baseline and at 6 months post-implant. The MSWS-12 was modified by substituting the effect of MS to the effect of pump implantation on 12 measures of ambulatory function.
LE	II-2
Number of Patients and Patient Characteristics	36 adult ambulatory patients with spasticity Ambulation was defined as the ability to walk at least 25 feet with or without the use of an assisted device • 19 males, 17 females • Age at initial pump implantation ranged from 19 to 66 years • 27 had multiple sclerosis (MS), 1 had primary lateral sclerosis (PLS), 2 had spinal cord injury (SCI), 6 had other neurological disorders, 31 of 36 patients had spinal spasticity, 5 were hemiparetic
Intervention	Continuous ITB infusion Medtronic programmable pump
Comparison	No comparator
Length of follow up (if applicable)	1 to 13 years
Outcome measures/ Effect size	Changes in pre and post ITB treatment (current post implant status) • Spasticity Assessment: ◦ All 36 patients had a reduced Ashworth spasticity score following pump implantation and ITB therapy • Long term ambulatory status: ◦ None of the 36 patients lost their ability to walk in the first 6 months of post implantation. ◦ 2 patients are now paraplegic, both with progressive MS, 1 deceased ◦ Of 33 patients that remain ambulatory, 4 patients need more assistance with ambulatory. There has been significant deterioration of their underlying disease. • Quality of Life (QOL) self-assessment: ◦ 34 of 36 patients (94%) retrospectively stated that they would have no reservations about receiving the implant again and were overall improved ◦ Based on the 12 items on QOL scale, only 2 patients (6%) had lower ambulatory score on one or more of the 12 items ◦ 21 of 36 patients (58%) had improved scores on every item considered ◦ ITB was beneficial in relieving pain in all 16 patients who had pain associated with spasticity **Authors conclusion** ITB therapy may be used in selected ambulatory patients with spasticity and is not associated with loss of ambulatory function.
General comments	Retrospective

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	39. Brochard S, Lempereur M, Filipetti P, Remy-Neris O. Changes in gait following continuous intrathecal baclofen infusion in ambulant children and young adults with cerebral palsy. Developmental Neurorehabilitation. 2009;12(6):397-405
Study Type / Methods	Pre and post intervention study conducted at two rehabilitation departments in France. The aim of the study was to assess the effect of continuous intrathecal baclofen infusion (ITB) on gait parameters of ambulant children with cerebral palsy (CP). The assessment before and after ITB on seven children with CP included: Ashworth scale score, range of motion (hip, knee, ankle), Gillette functional assessment questionnaire (FAQ), joint kinematics, spatiotemporal parameters and Gillette Gait Index (GGI). The GGI is the multivariate measure quantifying the degree of gait pathology and measures how closely an individual's gait pattern approaches typical gait. The GGI of a typical child is 15 with 95% percentile range of 8.20 to 26.90
LE	II-2
Number of Patients and Patient Characteristics	7 children with CP and were able to walk with or without an assistive device at least during physiotherapy sessions • 2 boys, 5 girls • Mean age was 15 years (SD, 5.40, range 9 to 22 years) • 4 were diplegics, 3 were quadriplegics • Gross Motor Function Classification – 3 as level II, 4 as level III • Before pump implantation, none of the patients underwent surgery Inclusion criteria: • Sufficient body mass to accommodate an ITB • Ashworth score ≥ 3 in at least 2 lower limb muscle group • Clearly defined attainment goal
Intervention	Continuous ITB infusion Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	16 months
Outcome measures/ Effect size	Changes before and after ITB treatment • Spasticity Assessment, Mean (SD): ◦ Global Ashworth score reduced after ITB from 3.04 points (SD, 0.85) to 1.89 points (SD, 1.21), $P < 0.05$ • Joint range: ◦ The only significant difference in joint angle measurements was increased rectus femoris range from 101.43 (SD, 14.64) to 118.57 (SD, 16.76), $P = 0.02$ • Postural control: ◦ 2 children who did not use walking aids before did not need one after ◦ 2 other children showed improved postural control (used less supportive walking aid after ITB) ◦ None need increased support after treatment • Gillette FAQ: ◦ Improved significantly from 6.10 (SD, 2.20) to 7.10 (SD, 2.00), $P = 0.02$ • Gillette Gait Index (GGI): ◦ Mean GGI improved from 554.50 to 489.25, which was not significant although the improvement was large for 3 children ◦ Parameters in the sagittal plane were significantly modified with a significant increase in step length from 0.65 (SD, 0.25 m) to 0.74 m (SD, 0.25), $P < 0.05$ **Authors conclusion** ITB seems to improve sagittal gait parameters of children and young adults with CP.
General comments	Retrospective

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	40. Bensmail D, Quera Salva MA, Roche N, Benyahia S, Bohic M, Denys P, Bussel B, Lafaso F. Effect of intrathecal baclofen on sleep and respiratory function in patients with spasticity. Neurology. 2006;67:1432-1436
Study Type / Methods	Pre and post intervention study conducted at the Hospital Raymond Poincare, France. The aim of the study was to prospectively evaluate the effect of pump-infused intrathecal baclofen infusion (ITB) in therapeutic doses on sleep quality and on day time and night time respiratory function in patients with severe spasticity. Prospectively included men and women older than 18 years who had severe intractable spasticity resistant to oral antispasmodic medications and requiring ITB therapy. One week before and at least 1 week after pump implantation, each patient underwent a physical examination including determination of Ashworth Scale score for spasticity and Penn Spasm Frequency score, polysomnography, pulmonary function testing, and determination of resting energy expenditure.
LE	II-2
Number of Patients and Patient Characteristics	20 patients • 15 men • 5 women • Mean age was 45 ± 13 years • Mean body mass index was 23 ± 5 kg /m2 • 9 patients had multiple sclerosis • 8 had SCI • 1 had cerebral palsy • 1 had hereditary spastic paraplegia • 1 had Friedreich ataxia
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	At least 8 days after pump implantation
Outcome measures/ Effect size	Changes before and after ITB initiation • Penn Spasm Frequency score, Mean ± SD: ◦ 3.75 ± 0.55 (range, 2 to 4) before ITB and 1.00 ± 0.56 (range, 0 to 2) after ITB initiation • Ashworth scale score, Mean ± SD: ◦ 2.75 ± 0.85 (range, 1 to 4) before ITB and 1.15 ± 0.36 (range, 1 to 2) after ITB initiation • Sleep studies: ◦ ITB improved total sleep time (P = 0.05) and sleep efficiency (P = 0.01) and reduced periodic leg movements (P = 0.02) ◦ ITB did not modify sleep-related respiratory events • Daytime lung function and resting oxygen consumption: ◦ ITB did not modify lung function tests, the CO_2 rebreathing response, or the resting energy expenditure **Authors conclusion** Compared with oral baclofen, intrathecal baclofen infusion did not affect respiratory function and improved sleep continuity. Intrathecal baclofen infusion in therapeutic doses may act at the spinal level rather than the supraspinal level.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	41. Vender JR, Hughes M, Highes BD, Hester S, Holsenback S, Rosson B. Intrathecal baclofen therapy and multiple sclerosis: outcomes and patient satisfaction. Neurosurg Focus. 2006;21(2):1-4
Study Type / Methods	Cross sectional study at the Multiple Sclerosis Centre of the Medical College of Georgia. The aim of the study was to provide an assessment of intrathecal baclofen (ITB) therapy and evaluate patient outcomes and satisfaction. Records for patients with multiple sclerosis who were selected as candidates for ITB therapy were reviewed for their response to test dose, surgical technique, surgery-and pump-related complications, and short and long term response to therapy. Patients were contacted and asked to complete a questionnaire designed to assess their overall satisfaction with ITB therapy. This was accomplished using a multipoint data collection tool designed to assess the overall response in four categories: activities of daily living (ADL), musculoskeletal, mobility and functional improvements. Each category included subcategories for additional insight. In cases in which patients were unable to respond, the primary caretaker was asked to assist in answering these questions. In addition special category for caretakers was included and focused on ease of care and decubitus ulcer incidence and recovery if applicable. In each subcategory, ratings were assigned on a scale of 1 to 9.
LE	II-3
Number of Patients and Patient Characteristics	33 patients with spasticity due to multiple sclerosis underwent implantation 20 patients completed the survey: • 80% females, 20% males • Mean age was 51 years • Patient who underwent implantation have had the pump for a mean of 31.9 months
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up duration was 31.9 months
Outcome measures/ Effect size	**Data Questionnaire; General overview** • Medications: ◦ 18 (90%) of the patients who completed the questionnaire were being treated with oral baclofen before receiving ITB therapy. After placement of ITB pump, 14 patients (77.7%) were able to discontinue oral baclofen, and 4 were able to decrease the dosages • Weight changes: ◦ 10 patients noted weight gain after pump placement with a mean gain of 19.3 lbs. Five patients noted weight loss, with a mean loss of 19 lbs • Recommend Pump and procedure: ◦ 70% said they would recommend the device for other patients, 15% said they would not, and 15% undecided • Response Categories: ◦ Changes in ADLs ◦ On average, no significant differences in ADLs (dressing, eating, grooming, toileting, and bathing) were noted after pump treatment • Musculoskeletal: ◦ Before the pump was implanted, patients stated on average, they had suffered spasms approximately 44.5% of the day, after the pump was implanted, this was reduced to 21% ◦ Patients comfort level rose from 4.7 before to 6.0 after the surgery • Mobility: ◦ Alterations in mobility did not occur after the surgery. Fine motor function coordination worsened after placement of the pump (could be explained by the progression of the disease) • Functional: ◦ Cognition did not change with pump placement ◦ Ability to sleep had improved to a score of 5.8 after surgery and a 6.0 on the day of the survey ◦ Self-esteem/body image had worsened after pump placement • Caregiver assessment (10 caregivers): ◦ Seven (70%) stated that the ability to take care for the patient after the pump placement was improved, two (20%) stated that care was unchanged, and one (10%) stated that the ability had worsened ◦ No patients suffered decubitus ulcers after pump placement **Authors conclusion** Intrathecal baclofen is safe and effective. Most patients and caregivers express satisfaction with the therapy and would recommend it to other patients. Spasm frequency appears to be the single most common variable positively affected by therapy.
General comments	

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Bibliographic Citation	42. Krach LE, Nettleton A, Klempka B. Satisfaction of individuals treated long-term with continuous infusion of intrathecal baclofen by implanted programmable pump. Paediatric Rehabilitation. 2006;9(3):210-218
Study Type / Methods	Cross sectional study at a regional specialty hospital for children and young adults with disabilities at the Gillette Children's Specialty Healthcare, St. Paul, USA. The aim of the study was to investigate the perspective of the individual receiving intrathecal baclofen (ITB) or his / her caregiver concerning effects and to describe characteristics of those that were satisfied or not satisfied. After IRB approval, potential subjects were identified who had undergone ITB pump implantation at least 1 year prior to the study. In order to be considered for the use of intrathecal baclofen at the institution, individuals must have an average Ashworth score of 3 or more in the lower extremities. One hundred subjects / caregivers were interviewed by phone. Interview consisted of a scripted questionnaire to obtain subject / caregiver opinions about changes in function and caregiver assistance, as well as satisfaction with ITB. Medical records were reviewed to collect information including diagnosis, ITB related surgeries and medications. Ratings / changes were classified as much better, somewhat better, no change, somewhat worse, much worse, and not applicable.
LE	II-3
Number of Patients and Patient Characteristics	100 subjects: Those who answered the survey included: • Mother of subject (59) • Father of subject (17) • self (10) • Nurse or other caregiver (9) • Foster mother (4) • Grandmother (3) • Grandfather (1) • Subjects ranged from 5 to 42 years of age, with a mean of 15 years. • 88 had Cerebral palsy • Mean time from pump implantation to interview was 2.6 years with a range of 1-3.75 years • All subjects had spasticity • 59 males, 41 females
Intervention	Continuous ITB infusion Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	
Outcome measures/ Effect size	• Goals of treatment: ◦ 71% reported they were fully met, 14% partially met and 15% either unsure or not met ◦ Improvement was noted in the following areas • Motor skills: ◦ 59% improved in ability to transfer, 74% in walking, 53% in use of arms, 70% ability to position • Ability to self-cares: ◦ 70% improved in dressing, 53% in toileting / hygiene, 48% in feeding • Child's emotion: ◦ 47% improved in general outlook in life, 40% in mood (emotions, attitude), 39% feel happy, 38% feel hopeful • Child's level of comfort: ◦ 55% improved in startle movements (sudden jerks), 54% in pain or discomfort, 43% sleeping at night • Ability to participate in activities: ◦ 57% improved participation in recreational activities, 44% in video or computer activities, 41% spend time exercising outside therapy, 40% family or residential activities • Satisfaction ◦ 82% indicated they would implant a pump again, 12% indicated that they would not and six uncertain **Authors conclusion** Generally, subjects and their caregivers were satisfied with the results after ITB pump implantation. A majority reported improvements in positioning, transfers, dressing, toileting / hygiene and comfort.
General comments	

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Bibliographic Citation	43. Krach LE, Kriel RL, Gilartin RC, Swift DM, storrs BB, Abbott R, Ward JD, Bloom KK, Brooks WH, Madsen JR, McLaughlin JF, Nadell JM. Hip status in cerebral palsy after one year of continuous intrathecal baclofen infusion. Pediatric Neurology. 2004;30(3):163-168
Study Type / Methods	Prospective, non controlled, open-label, multi centre study conducted in the USA (pre and post intervention study). The aim of the study was to assess whether reduction of muscle tone by continuous intrathecal baclofen infusion affects the progression of hip subluxation in persons with cerebral palsy. This prospective, open label case series was conducted at multiple speciality referral centres. There were 33 subjects, all had pre treatment lower extremity Ashworth score of ≥ 3; all subjects had a significant reduction in tone after a bolus injection of intrathecal baclofen and received an implanted pump for continuous deliver of intrathecal baclofen. Subjects had hip x-rays before and 1 year after pump implantation. The primary outcome measure was change in absolute hip migration percentage of 5% or more. Increases of 5% or more were classified as worsening condition; decreases from pre study measurements of 5% or more were classified as improvement, changes within 5% or more were classified as no change.
LE	II-2
Number of Patients and Patient Characteristics	33 subjects • 20 (60.6%) males • Mean age was 12.1 with a range of 4 to 31.4 years; median age was 10.3 years • 24% had diplegic CP, 64% had quadriplegic CP, 12% had paraplegic CP • 73% non ambulatory, 18% totally dependent for activities of daily living Inclusion criteria: • 3 years and older with sufficient body mass to accommodate an implantable pump • Diagnosis of spastic CP and Ashworth score ≥ 3 in their legs • Completed double blind study and demonstrated a favourable response to ITB
Intervention	Continuous ITB infusion. SynchroMed™ Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	Status of Migration 1 year after baclofen infusion • Change in absolute migration percentage of 5% or more: ◦ 12.1% of hips in all cerebral palsy classifications improved ◦ 33.3% manifested progression in hip subluxation ◦ 54.5% of hips remained unchanged • Change of migration percentage class: ◦ Overall, 90.9% of hip manifested no deterioration or had improvement of their migration percentage class during the year of intrathecal baclofen therapy • The observed changes were not associated with the subject's age or severity of cerebral palsy
General comments	Industry sponsored

Evidence Table : EFFECTIVENESS
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Bibliographic Citation	44. Silva S, Nowicki P, Caird MS, Hurvitz EA, Ayanggar RN, Farley FA, Vanderhave KL, Hensinger RN, Graig CL. A comparison of hip dislocation rates and hip containment procedures after selective dorsal rhizotomy versus intrathecal baclofen pump insertion in nonambulatory cerebral palsy patients. J Pediatr Orthop. 2012;32(8):853-856
Study Type / Methods	Comparative study conducted at one institution. The aim of the study was to compare the rate of hip dislocation and the need for further hip surgeries in selective dorsal rhizotomy (SDR) and intrathecal baclofen pump (ITBP) patients. All non ambulatory cerebral palsy patients who had either SDR or ITBP and had minimum follow-up of 2 years were retrospectively reviewed for demographic data and timing, total number, and type of hip procedures (soft tissues versus bony) and occurrence of hip dislocation. Hip dislocation was defined as complete loss of contact between the articular surface of the femoral head and the acetabulum.
LE	II-2
Number of Patients and Patient Characteristics	119 spastic quadriplegic cerebral palsy patients • SDR group = 69 patients: ◦ 40 males, 29 females ◦ Average age at time of surgery (6 year 11 months) range, (30 to 220 months) • ITBP group = 50 patients ◦ 27 male, 23 female ◦ Average age at time of surgery (9 year 8 months) range, (37 to 222 months)
Intervention	Continuous ITB infusion [intrathecal baclofen pump(ITBP)]
Comparison	Selective dorsal rhizotomy (SDR)
Length of follow up (if applicable)	Minimum 2 years
Outcome measures/ Effect size	ITBP group versus SDR group • Hip dislocation rate: ◦ 10.6% (10/94) in the SDR group ◦ 7.4% (7/94) in the ITBP group • Secondary hip containment surgery rate: ◦ 25% (35/138) in the SDR group ◦ 32% (32/100) in the ITBP group Overall, 36.2% (25/69) of patients in the SDR group had either a hip dislocation and / hip containment surgery as compared with 46% (23/50) patients in the ITBP group. • Total of 19 hip procedures in the SDR group and 20 in the ITBP group (P = 0.15) • 17 soft-tissue procedures were performed in both SDR and ITBP groups (P = 0.265) • 6 bony procedures were performed in the SDR group and 10 in the ITBP group (P = 0.075). **Authors conclusion** There was no significant difference in the rate of secondary hip reconstructive surgery or dislocation between non ambulatory cerebral palsy patients who underwent SDR versus ITBP. Reconstruction was required in 25% to 32% of hips despite spasticity intervention with either procedure. This suggests that the L1 nerve root alone does not play a major role in the progression of hip dislocations.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity?

Bibliographic Citation	45. Krach LE, Kriel RL, Day SM, Strauss DJ. survival of individuals with cerebral palsy receiving continuous intrathecal baclofen treatment: a matched-cohort study. Developmental Medicine & Child Neurology. 2010;52:672-676
Study Type / Methods	Matched cohort study at Gillette Children's Specialty Healthcare in St Paul, MN, USA. The aim of the study was to determine whether intrathecal baclofen (ITB) changes mortality risk in persons with cerebral palsy (CP). Records were reviewed for all persons with CP who were managed with ITB for hypertonicity at a specialty hospital in Minnesota between May 1993 and August 2007. A comparison cohort with CP was randomly selected from clients of the California Department of Developmental Services who were initially evaluated between 1987 and 1990 and were matched to those with ITB for age, sex, Gross Motor Function Classification System (GMFCS) level, presence or absence of epilepsy, and feeding tube-use. Survival probabilities were estimated using the Kaplan-Meier method, and differences were tested via log-rank.
LE	II-2
Number of Patients and Patient Characteristics	• 359 persons with CP who received ITB for hypertonicity ◦ 202 males ◦ 157 females ◦ Mean age was 12 years 8 months, (SD 7 years 9 months), range; 3 years 1 month to 39 years 9 months • 349 persons with CP without ITB pumps ◦ 195 males, 154 females ◦ Mean age was 12 years 7 months, (SD 8 years 4 months), range; 2 years 7 months to 40 years
Intervention	Continuous ITB infusion
Comparison	Without ITB pump
Length of follow up (if applicable)	Mean follow-up was 6 years 2 months (SD, 3 year) in the Minnesota ITB cohort Mean follow-up was 6 years 2 months (SD, 2 year 6 months) in the California non ITB cohort
Outcome measures/ Effect size	Survival • During the follow-up there were 21 deaths in the Minnesota ITB cohort and 50 deaths in the California non-ITB cohort • Survival at 8 years of follow-up was 92% (SD, 1.9%) in the Minnesota ITB cohort and 82% (SD, 2.4%) in the California non ITB cohort, $P < 0.001$. After adjustment to account for recent trends in improved survival in CP, 8-year survival in the non-ITB cohort was 88%, which was not significantly different from the ITB cohort ($P = 0.073$) **Authors conclusion** ITB therapy does not increase mortality in individuals with CP and may suggest an increase in life expectanc
General comments	Industry sponsored

Evidence Table : SAFETY
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Bibliographic Citation	1. Hoving MA, van Raak E P.M, Spincemaille GHJJ, van Kranen-Mastenbroek VHJM, Kleef Mv, Gorter JW, Vles JSH. Safety and one-year efficacy of intrathecal baclofen therapy in children with intractable spastic cerebral palsy. European Journal of Paediatric Neurology. 2009;13:247-256.
Study Type / Methods	Prospective follow-up study of randomised controlled trial conducted at the University Hospital Maastricht in the Netherlands. The aim was to study the efficacy at 12 months and safety up to 24 months after the start of continuous intrathecal baclofen infusion (CITB) in children with intractable spastic cerebral palsy (CP). Nine girls and 8 boys received Synchromed pump for continuous infusion of intrathecal baclofen. The effects and adverse events were prospectively recorded at regular follow-up visits (3- month) up to 24 months. Outcome measures included the 0-10 visual analogue scale (VAS) for individual problems, Gross Motor Function Measure (GMFM) and health related quality of life as measured with the Child Health questionnaire –PF50. Adverse events were recorded on standardised forms. Adverse event was defined as any undesirable experience occurring to a participant during the study. A serious adverse event was defined as any untoward medical occurrence or effect that: (1) resulted in death; (2) was life threatening; (3) required hospitalisation or prolongation of existing hospitalisation; or (4) resulted in persistent or significant disability or incapacity. Non-parametric Wilcoxon Signed Rank Test was used to compare the results of the outcome measures at the 6-month and 12-month follow-up visit with those at baseline. Baseline measurements were carried out before pump implantation.
LE	II-2
Number of Patients and Patient Characteristics	17 children, 9 girls and 8 boys participated in the Dutch ITB study: Aged 13.7 years (SD, 2.9; range 7 to 17) at the time of pump implantation
Intervention	Continuous ITB infusion and standard treatment
Comparison	No comparator
Length of follow up (if applicable)	24 months
Outcome measures/ Effect size	**Adverse events:-** Recorded adverse events for mean duration of 18.4 months (range 12 to 24 months) Non-procedure or device related adverse events: • 14 of 17 children experienced a total 51 non-procedure or device related adverse events during a follow-up of 312 patient-months [incidence 0.16 per patient-month (95% CI: 0.12 to 0.20)] • 24 different events were reported • Most frequently observed event was lethargy, which occurred in 8 children. The lethargy either disappeared spontaneously or after slightly reducing the CITB dose. • Temporary pressure sores were noted in 4 children, at the toe, foot, hip, and ear respectively • Nausea, vomiting, excessive hypotonia and / or decreased appetite mainly occurred during the first postoperative days and seemed related to taking oral baclofen simultaneously with CITB. • 5 of the 51 non-procedure or device related adverse events were considered serious, because they resulted in significant disability. One was difficulty swallowing, 1 dysarthria, 2 excessive hypotonia, 1 epileptic seizure. None of the adverse events was life-threatening and no hospitalisation was necessary. Procedure or device related adverse events: • 14 of 17 children experienced a total of 29 procedure or device adverse events during a follow-up of 312 patient-months [incidence: 0.09 per patient-month (95% CI: 0.06 to 0.12)]. • One third of these events concerned swelling at the pump or catheter insertion site. Except for one, these swellings always resolved either spontaneously or with a temporary pressure dressing. • 3 out of the 29 events were considered serious, because these children required a second operation resulting in a prolonged hospital stay (1 incomplete operation, 1 abrupt lack of CITB effect and 4 pain at pump site) • None of the children had a wound infection or meningitis and none of the pumps had to be removed **Authors conclusion** The authors concluded that CITB was effective at 12 months and safe up to 24 months for carefully selected children with intractable spastic CP. CITB relieved pain, facilitated ease of care and improved mental health. The majority of children could extend their activities and participation.
General comments	

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Bibliographic Citation	2. Gilmartin R, Bruce D, Storrs BB, Abbot R, Krach L, Ward J, Bloom K, Brooks WH, Johnson DL, Madsen JR, McLaughlin JF, Nadell J. Intrathecal baclofen for management of spastic cerebral palsy: multicenter trial. 2000;15:71-77.
Study Type / Methods	Phase 1, double blind placebo controlled trial (screening phase) Phase 2, open label (long-term infusion phase) Study was conducted in 12 centres, in the United States of America (U.S.A) initiated in 1992 The aim of this study was to assess the safety and efficacy of continuous intrathecal infusion of baclofen in patients with spastic cerebral palsy. Phase 1 involved a double-blind intrathecal bolus of 50 µg of Lioresal intrathecal (baclofen injection) or placebo (0.9% preservative-free sodium chloride injection), delivered by lumbar puncture, percutaneous spinal catheter, or implanted port with spinal. Oral baclofen was stopped prior to study participation unless discontinuation presented a hazard to the patient. The patients were assigned to a baclofen-placebo or a placebo-baclofen sequence with a 48-hour washout period between injections. The investigator, evaluator, patient, and caregiver were blinded to treatment regimen. All patient were monitored for safety and efficacy during the 3-day in patient period. The Ashworth Scale was used to quantify spasticity at baseline and 0.5, 1, 2, 4, 6, 8, and 24 hours after the bolus was delivered. The study blind was broken 12 to 24 hours after the second bolus. For those patients who received baclofen, a reduction of one point in the average Ashworth Scale score for all eight lower-extremity sites, maintained over two successive measurements between the 1 and 8 hour periods, identified them as candidates for pump implantation. Phase 2 consisted of an open-label, long-term, intrathecal infusion of baclofen. Clinical objective of phase 2 was to maintain an average Ashworth Scale score in lower extremities of 1 or 2, or to maintain optimal function. The study protocol required 10 routine visits in the first year following implantation. Spasticity was evaluated within 2 weeks of implantation, monthly for 6 months, and then at 3 month intervals.
LE	II-I
Number of Patients and Patient Characteristics	Phase 1 trial: 51 patients enrolled in the • 29 male, 22 female • Age; range (-4 to 31.3 years), mean age (10.3 years), median age (11.2 years) • 4 had spastic paraplegia, 12 had spastic diplegia, 35 had spastic quadriplegia Phase 2 trial: • 44 patients received implants Inclusion criteria: • Age 3 years or older • Enough body mass to accommodate an implantable pump • Severe spasticity, Ashworth scale score of 3 or more in the lower extremity measurements
Intervention	Phase 1: Intrathecal bolus baclofen injection Phase 2: Intrathecal infusion of baclofen
Comparison	Phase 1: Placebo; 0.9% preservative free sodium chloride injection. Phase 2: No comparator
Length of follow up (if applicable)	Mean: 27.8 months, Range: 4.0 to 43.2 months
Outcome measures/ Effect size	**Adverse events** Of the 51 patients enrolled in the study, 42 reported 205 adverse events while on the intrathecal baclofen. All patients recovered uneventfully. Adverse Events During Drug Exposure Occurring In More Than 2% of Patients:- • Screening phase (double-blind bolus dose period): ◦ Placebo injection: 7 adverse events occurred during the placebo injection (3 headache, 2 vomiting, 2 nausea) ◦ Baclofen injection: somnolence (5), nausea / vomiting (5), vomiting (3), headache (2), hypotonia (1), nausea (1), dizziness (1) • Titration phase (1st 60 days after implantation): ◦ Hypotonia (14), somnolence (6), vomiting (5), seizure (4), increased salivation (4), headache (3), nausea /vomiting (3), nausea (2), dizziness (1) • Maintenance phase (60 days after implantation and beyond): ◦ Hypotonia (16), seizure (15), headache (9), somnolence (7), vomiting (6), nausea (5), dizziness (4), increased salivation (2), nausea / vomiting (1) • Total drug events: (31), seizure (19), somnolence (18), headache (14), vomiting (14), nausea / vomiting (9), nausea (8), dizziness (6), and increased salvation (6). • All patients who experienced seizures had a history of seizures. No seizures were reported in the screening phase of the study. **Device adverse events** Device adverse events were defined as any adverse event associated with surgical technique, system components, or refilling or programming errors. 30 (65.2%) patients with devices experienced 59 device adverse events classified either as related to the procedure (occurring in the first 60 days after implantation and not directly attributed to the device) or to the system (occurring beyond the first 60 days after implantation and not attributed to a procedure) Of the 59 device adverse events, 39 were related to the procedure and 20 were related to the system. No. of events (IR=incidence per patients year of follow-up): • Most common procedure related adverse events were pocket seroma 7 (IR =0.07), pocket infection 5 (IR=0.05), catheter dislodged 4(IR=0.04), cerebrospinal fluid leaks 3 (IR = 0.03) and other 20 • Most common system related problems consisted of catheter break 2 (IR=0.02), catheter dislodged 2 (IR=0.02), back pain at catheter site 2 (IR=0.02) and other 14.
General comments	

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Bibliographic Citation	3. Van Schaeybroeck P, Nuttin B, Lagae L, Schrijvers E, e Borghgraef C, Feys P. Intrathecal baclofen for intractable cerebral spasticity: A prospective placebo-controlled, double-blind study. Neurosurgery. 2000;46(3):603-612
Study Type / Methods	Randomised, double blind placebo controlled trial (screening phase) Open label (long-term infusion phase) Study was conducted at the University Hospital Gasthuisberg, Leuven, Belgium. The aim of this study was to;1) examine the effect of intrathecal baclofen (bolus injections and continuous infusion), 2) demonstrate functional improvement in severely disabled patients, 3) evaluate the effect on spasticity in different muscle groups **Screening** The screening trial was performed in a placebo-controlled fashion. A lumbar puncture was performed once daily, and injections of 25, 50, 75 or 100 µg of baclofen or saline were given in random order, starting with either 25 or 50 µg of baclofen or saline. The patient, family, and physical therapist were blinded to the bolus dose and the placebo injection. Spasticity was scored using the Ashworth scale and a visual analog score (VAS). A large range of muscle groups were evaluated using Ashworth scale by two experienced physical therapists. The "baseline spasticity score" was calculated as the mean spasticity score of all baseline evaluations during the screening period. After bolus injections with baclofen, evaluation was performed at 2, 4, and 6 hours. The VAS was calculated on the basis of a 10 cm line representing 0 to 100% severity of spasticity, on which the patients or their caregivers marked their perceived spasticity score. Implantation, follow-up, and dose reduction test. Eight patients underwent implantation of SynchroMed Infusion System programmable pump (Medtronic, Inc., Minneapolis, MN). The minimal effective bolus injection dose was doubled to calculate the starting chronic infusion dose. Outpatient follow-up was organised at 1,3,6,9, and 12 months, and thereafter according to the refilling requirements of the pump. During the first year of follow-up each patient was subjected to a blinded dose reduction test and (with the exception of one patient) to subsequent physiotherapeutic and subjective scoring.
LE	II-I
Number of Patients and Patient Characteristics	Screening phase: 11 patients enrolled in the study: • Patients with spasticity of cerebral origin (mainly cerebral palsy) • 5 females, 6 males • Patients were severe quadriparesis, as well as those with relatively good motor function Implantation, follow-up, and dose reduction test: • 8 patients (6 patients follow-up for 2 years) • 4 of the six patients who received implants were extremely disabled, wheelchair bound, and mentally retarded Inclusion criteria: • Severe quadriparesis • Relatively good motor function • Treatment with oral antispasmodic was either inefficient or provoked intolerable side effects Exclusion criteria: • Child bearing potential • Pregnancy • Renal or hepatic dysfunction
Intervention	Screening phase: Intrathecal bolus baclofen injection Implantation, follow-up, and dose reduction test: Intrathecal infusion of baclofen
Comparison	Screening phase: Placebo; Saline. Implantation: No comparator
Length of follow up (if applicable)	2 years
Outcome measures/ Effect size	Adverse events: • One patient (Patient 2) had somnolence during 12-hour period after a bolus injection of 100 µg of baclofen • One mechanical complication: 1 year after the initial implantation, the catheter was disconnected at the pump in patient 5 • No seizures were provoked by the treatment, and in Patient 2 the antiepileptic treatment had been simplified, which resulted in better control of seizures
General comments	

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Bibliographic Citation	4. Meythaler JM, Guin-Renfroe S,Brunner RC, Hadley MN. Intrathecal baclofen for spastic hypertonia from stroke. Stroke. 2001; 32:2099-2109
Study Type / Methods	Randomised, double blind placebo controlled, cross over trial (screening phase). Open label (long-term infusion phase). Study was conducted at the tertiary care university medical centre (Alabama School of Medicine, Birmingham, Alabama). The aim of this study was to determine whether continuous intrathecal delivery of baclofen can effectively decrease spastic hypertonia due to stroke. **Screening** Patients were randomised before the bolus to either 50 µg baclofen or preservative free normal saline via a coin toss. All boluses were at least 72 hours apart. Those who dropped an average of 2 points in either their affected lower extremity side Ashworth or Penn spasm frequency scores were then offered computer-controlled pump implantation for continuous ITB and followed prospectively for up to 12 months. Patients who had a partial drop (< 2 points) in the mean Ashworth scores or Penn spasm frequency scores but did not meet criteria for pump placement were given the option of a 75-to 100-µg bolus trial, which was not blinded. If, after this trial, they qualified the pump placement was offered. Both the raters and the patients were blinded until after the second bolus. **Implantation** After implantation of the continuous infusion device, patients were followed on an outpatient basis for refilling and dosage adjustment. The 5-point Ashworth (rigidity) scale was used to assess muscle tone in both lower extremities. A 4-point scale which reflected the number of spontaneous sustained flexor and extensor muscle spasms per hour was used. A 5-point scale documenting deep tendon reflexes was used at the biceps, patella and Achilles. The statistical study design is an A-B single case control design with each patient used as his or her own control. Data are presented as averages with standard deviations. Rather than consider each muscle separately, average scores for muscle tone, spasms, and reflexes were averaged for the upper extremities or lower extremities for each patient.
LE	II-I
Number of Patients and Patient Characteristics	**Screening** 21 subjects • Average age = 53 years, range (16 to 86 years of age) Criteria for inclusion in the study: • > 16 years of age • Diagnosis of severe chronic spastic hypertonia in the lower limbs for at least 6 months duration that was defined by an average Ashworth score of at least 2 in the affected extremities at the day of the first screening • Failure to respond satisfactorily to treatment with maximum recommended doses of oral antispasticity medications or the occurrence of unacceptable side effects at effective treatment dosages **Continuous Infusion of ITB** 17 adult CVA patients • Average age = 50 years, range (16 to 86 years) • All patients were > 6 months from the onset of stroke (mean 41 months, range 10 to 107 months) • 4 followed up for 6 months, 13 were followed up for 1 year • 11 were right CVA patients with left hemiparesis, 4 were left CVA with right-sided hemiparesis, 2 were brain stem stroke patients with quadriparesis
Intervention	Screening: Intrathecal bolus baclofen injection 50 µg Implantation: Intrathecal infusion of baclofen
Comparison	Screening: Placebo; preservative free normal saline injection. Implantation: No comparator
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**Adverse events** Bolus trial: • There was no adverse effects from the bolus other than a headache in 2 patients that lasted 24 to 48 hours. • No patient suffered any serious adverse effects from withholding any oral antispasticity medications before the bolus Continuous Infusion of ITB for up to 1 year: • Five patients had changes in urinary voiding patterns with initial pump placements, all related to urinary retention. With a reduction in ITB dosage, this resolved and did not return despite later dosage increases. • Postoperative headaches with nausea were transient in several patients. The headaches were treated conservatively by keeping the patient supine for a day and with the administration of intravenous fluid. The headaches were felt to be due to a CSF leak associated with catheter placement. • No patient developed seizures after pump placement, nor was there a history of seizures in any of these patients prior to pump placement. • No infections or meningitis as a result of pump and catheter placement. • One patient gained 40 lb after pump placement. The increased abdominal circumference resulted in the catheter backing out of the intrathecal space approximately 1 year after pump placement. The system was revised without difficulty.
General comments	Received grant for the study from Medtronic

Evidence Table : SAFETY
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Bibliographic Citation	5. Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. J Neurosurg. 1996;85:452-457
Study Type / Methods	Pre- and post-intervention study conducted at Boston University Medical Centre. The aim of the study was to determine the efficacy, safety, and cost-effectiveness of intrathecal baclofen delivered by a programmable pump for the chronic treatment of severe spasticity. 69 patients with severe spasticity of spinal cord origin that was refractory to oral baclofen or who experienced intolerable side effects with this form of the drug were screened. The first nine participated in a double-blinded, randomised, placebo (normal saline) controlled trial to determine response to a bolus dose of ITB. Subsequent patients were enrolled in an open-labelled treatment protocol without a placebo trial. All passed the screening and the pump was implanted in 59 patients. Spasticity scores and medical costs before and after surgery were analysed.
LE	II-2
Number of Patients and Patient Characteristics	66 patients with intractable spasticity of spinal origin. Of these, 59 underwent implantation. • 27 had SCI • 26 has MS • 2 had familial spastic paraparesis • 4 others • 35 males • 24 females • Mean age = 42 years (ranged, 16 to 73 years) Severe spasticity defined as Ashworth score of 3 or higher or spasm score of 2 or higher.
Intervention	Continuous ITB infusion and standard treatment A programmable pump (SynchroMed Infusion System; Medtronic)
Comparison	No comparator
Length of follow up (if applicable)	Mean; 42 months (range, 23 to 70 months)
Outcome measures/ Effect size	**Drug tolerance:** • Drug tolerance in 1 patient with MS 21 months after the pump implanted. Dose of ITB administered increased from 520 to 800 µg daily over a 2-month period. Radiographic and radionuclide studies showed the system to be patent. He was given a 1-month drug holiday from intrathecal baclofen, during which he received 2 mg of intrathecal morphine daily. When intrathecal baclofen was resumed, he had an excellent response to 100 µg daily. **Treatment complications:** • Six patients with pre-existing constipation were more symptomatic post surgery. All responded to a vigorous bowel regimen consisting of enemas and suppositories. • Muscular hypotonia in 3 ambulatory patients, urinary retention in 3 others, and nausea, dizziness, and drowsiness in one patient responded to a decrease in dosage. There was no respiratory depression and no coma. • Problems with intrathecal catheter occurred 19 times in 15 patients. Consisted of 7 breaks in 5 patients, 9 occlusions, 2 punctures, and 1 dislodgement. • Two pumps were explanted, one because of infection in the pump pocket and the other because of skin erosion. • One CSF leak was treated with laminectomy and repair of the dura. • No pump failures.
General comments	

Evidence Table : SAFETY

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Bibliographic Citation	6. Natale M, Mirone G, Moraci RA. Intrathecal baclofen therapy for severe spasticity: Analysis on a series of 112 consecutive patients and future prospectives. Clinical Neurology and Neurosurgery. 2012;114:321-325
Study Type / Methods	Pre- and post-intervention study conducted at Second University of Naples SUN, Naples, Italy. The aim of the study was to discuss new indications and screening tools, appropriate surgical timing and compliance avoidance. Between 2/9/2000 and 31/12/2007, a total of 65 consecutive patients all with severe, progressive and refractory to medical therapy spasticity from different causes were evaluated intrathecal baclofen infusion after signature of informed consent. The other 47 patients were referred to the neurosurgery department after the implantation in two secondary centres for refilling of the pumps, daily dose titration and clinical follow-up. The neurological conditions were evaluated by the Modified Ashworth Scale (MAS) for the rigidity which was performed by two experienced physical therapists. The MAS scale was assessed for every patient before and after test and at follow-up time. The Penn Spasm frequency scale (SFS) was used for evaluating the spasms frequency in both the lower and the upper extremities. Pain was measured on a 10 point self assessment Visual Analogical Scale (VAS) with a score ranging from 0 to 10, where 0 means no pain and 10 means having unbearable pain. Ambulatory patients underwent preoperative instrumented gait analysis prior to and 4 hour following the screening test. The bolus screening (ranging from 25 µg to 100 µg was administered by a lumbar puncture at L3 ± L4 interspaces. Response was considered positive if there was an improvement of two or more points in the Ashworth scale for at least 4-6 h after the test. In case of positive response, a continuous infusion pump (Synchromed or Synchromed II, Medtronic Inc., Minneapolis, MN USA) was implanted.
LE	II-2
Number of Patients and Patient Characteristics	112 patients: • 63 males (56%), 49 females (44%) • Average age = 43.2 years (range; 7-63 years) • 74 (66%) had quadriparesis • 34 (30.4%) had a paraparesis • 4 (3.6%) were hemiplegic • 77 (68.7%) were non ambulatory, while 35 (31.3%) were ambulatory Causes of spasticity: • Multiple sclerosis (25 cases) • Cerebral palsy (21 cases) • Traumatic brain injury (10 cases) • Anoxic acquired brain injury (12 cases) • Spinal cord injury (15 cases) • Familial paraparesis (7 cases) • Friederich's ataxia (4 cases) • Adrenal leukodistrophy (3 cases) • Amyotrophic lateral sclerosis (4 cases) • Transverse myelitis (8 cases) • Syringomyelia (2 cases) • Rigid spine syndrome (1 case) Inclusion criteria: • Chronic severe disabling spasticity (score > 3 in the MAS) inhibiting or influencing personal care, sitting, lying, and transfers, accompanied by pain and stiffness, or disturbed sleeping • Failure of oral antispastic drugs • Absence of block in cerebrospinal circulation • No allergy to medication or pregnancy • Positive response to bolus intrathecal administration
Intervention	Continuous ITB infusion and standard treatment All patients started with simple continuous infusion after surgery. Complex infusion was selected in 56 patients (5)%), from 3 to 27 months (mean 14 months) after surgery. Medications used: Baclofen, 2000 µg/ml (95 patients), Baclofen, 500 µg/ml (15 patients), Morphine 10 mg/h with baclofen 1000 µg/ml (1 patient)
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up time; 55 months (range: 12 to 72 months)
Outcome measures/ Effect size	**Adverse events:** • No mortality, nor permanent morbidity related to ITB, and in addition no patient developed new neurologic deficit as a result of treatment • Drug induced complication was observed in 7 patients (6.3%): ◦ 4 patients (3.6%) developed tolerance and they were weaned and kept off ITB for four to six weeks drug holiday. During this time intrathecal morphine was administered. When ITB was restarted, the effective dose was less than half the dose to which they had been tolerant and this low dose has been continued for 3 to 4 months before requiring an increase. ◦ Nausea, dizziness, and drowsiness in 1 patient (0.9%) ◦ Hypotension and bradycardia in 2 patients ◦ Function returned after dose reduction or transient interruption of ITB • 10 catheter problems (8.9%) occurred: ◦ 2 occlusions (and kinks) ◦ 3 breaks ◦ 5 dislodgements • There were 2 (1.8%) pocket infections and 2 (1.8%) skin erosions mainly due to decubitus • Pumps were explanted from nine patients (8%) who withdrew from therapy for the following reasons: ◦ Marked reduction of spasticity (3 cases) ◦ Pocket infection (2 cases) ◦ Skin erosion (2 cases) ◦ Aesthetic reasons (2 cases)
General comments	Pain score result not reported.

Evidence Table : SAFETY
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Bibliographic Citation	7. Gray N, Morton RE, Brimlow K, Keetley R, Vloeberghs M. Goals and outcomes for non ambulant children receiving continuous infusion of intrathecal baclofen. European Journal of Paediatric Neurology. 2012;16:443-448
Study Type / Methods	Pre- and post-intervention study conducted at the National Nottingham ITB service, United Kingdom. The aim of the study was to evaluate the success of goals and compare these to actual outcomes in severely disabled children receiving continuous ITB. The participants were also part of a controlled prospective study of ITB in children, which also investigated function, participation in society and quality of life. Children attending the national Nottingham Children ITB service were recruited from 2003 to 2007 who met the following inclusion criteria: They were to be fitted with an UTB pump on the basis of severe spasticity that reduced function, caused pain or interfered with the ease of care Had a diagnosis of cerebral palsy, were non ambulant; GMFCS groups IV-V, aged 5 to 15 years Able to be assessed at three specific times, before pump fitment, then 9 and 18 months after Prior to pump insertion, 3 specific goals were set between the caregiver, physiotherapist and if possible the child. Goals included function, ease of acre, mood, or prevention of deformity. The goals were set as a simple statement implying overall benefit in all aspects. These were reviewed at the assessments, together with caregivers' views of the outcome of treatment in 14 different aspects. At the first and the last assessment, the degree of deformity of the hips and spine were reviewed, and orthopaedic surgeons were asked to predict what surgery would be needed in the next 2 years.
LE	II-2
Number of Patients and Patient Characteristics	37 children: • 19 males, 18 females • Mean age (SD) = 10.16 (3.25) years • Median age (range) = 10.0 (3 to 15) GMFCS level: • 18 level IV, 19 level V CP type: • 13 diplegia • 24 quadriplegia Dyskinesia present: 6
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	18 months
Outcome measures/ Effect size	Side effects of ITB: • Over 18 months, 20 children reported a total of 21 side effects at 9 months, 4 of which were still present at 18 months • The most common was constipation reported in 9 children at 9 months, and remaining in 2 at 18 months Adverse events over 18 months for 37 children: • Swelling in the back at the catheter site (1) • Kinked catheter (1) • Undiagnosed malfunctioning system (1) • Catheter cut during scoliosis surgery (1) • Catheter split (1) **Authors conclusion** The authors concluded that ITB is a major treatment for children with severe disability and should be undertaken with understanding of what can and cannot be achieved, before allowing realistic goals to be set.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	8. UCAR T, Kazan S, Turgut U, Karaman Samanci N. Outcomes of Intrathecal Baclofen (ITB) therapy in spasticity. Turkish Neurosurgery. 2011;21(1):59-65
Study Type / Methods	Pre- and post-intervention study conducted at Akdeniz University, Antalya / Turkey. The aim of the study was to evaluate the long-term efficacy of intrathecal baclofen on the spasticity and pain, and to evaluate the side effects of intrathecal baclofen. The medical records of 30 patients who underwent baclofen pump placement from 2000 to 2010 under the Department of Neurosurgery and followed up at the Department of Physical Medicine and Rehabilitation at Akdeniz University, Antalya / Turkey were reviewed. After signing an informal consent form for ITPB therapy, patients underwent a screening procedure to determine responsiveness to ITB. All subjects were given a test bolus 50 µg baclofen by lumbar puncture. The response was considered positive is there was an improvement of two or more points on Ashworth scores. In case of positive response, a continuous infusion pump was implanted. All patients were evaluated before the treatment, during the intrathecal bolus test with ITB, and follow-up period (two months after the pump implantation, then every 3 months). Patients' evaluation was done using spasticity measures (Ashworth scale). Activities of daily living were measured using the Barthel Index preoperatively and the following year. Handicap was measured by the Rankin Scale. Pain was assessed with a self-reported visual analogue scale from 0 to 10.
LE	II-2
Number of Patients and Patient Characteristics	30 patients: • 19 males, 11 females • Mean age = 30.10 ± 16.09 years • All study subjects had diffuse chronic, severe, and generalise spasticity of at least 3 months duration (Ashworth score ≥ 3), and had failed to respond adequately or had experienced untoward side effects from various oral antispastic drugs included baclofen Aetiology of spasticity: 18 supraspinal spasticity (Cerebral palsy / brain injury),12 had (Spinal Cord Injury)
Intervention	Continuous ITB infusion All patients started with simple continuous infusion after surgery. Complex infusion was selected in 56 patients (5%), from 3 to 27 months (mean 14 months) after surgery. Medications used: • Baclofen, 2000 µg/ml (95 patients) • Baclofen, 500 µg/ml (15 patients) • Morphine 10 mg/h with baclofen 1000 µg/ml (1 patient)
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up period; • 27.60 ± 14.66 months (range: 1 to 62 months) • 5 patients treated for more than 48 months, 8 more than 36 months
Outcome measures/ Effect size	**Complications:** • 1 infection in young adult. The pump was removed and a new pump was reimplanted 3 months later. • Systemic infection has not been identified in any cases. • Most common surgical complication was cerebrospinal fluid collection. Mostly seen in paediatric patient groups, and was treated in a short time with an elastic bandage rather than any extra processes. • Most common identified technical complication was a broken or retracted catheter, [5 cases (16.6%)]. **Authors conclusion** The authors concluded that ITB therapy increases the quality of lifestyle and functional independence by reducing not only cerebral but also spinal related spasticity in appropriately selected cases.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with for spasticity?

Bibliographic Citation	9. Gluglielmino A, Sorbello M, Fazzio S, Zingale SF, Bucolo GE, Pittala G, Castiglione A, Patti F, Mangiamfli S. Continuous intrathecal baclofen administration by a fully implantable electronic pump for severe spasticity treatment: our experience. Minerva Anestesiol. 2006;72:807-820
Study Type / Methods	Pre- and post-intervention study conducted at University Hospital of Catania, Italy. The aim of the study was to evaluate the efficacy of continuous intrathecal baclofen infusion delivery by a programmable pump for severe spasticity according to patient selection criteria, implantation technique and related parameters, and outcome after the initial follow-up period. Intrathecal baclofen infusion was initiated in 30 patients within 24 hour after a test dose of the agent resulted positive in spinal anaesthesia. During the procedure and the follow-up period, the following parameters were measured: incidence of anaesthesiological or surgical complications and adverse events, postdural puncture headache, prolonged motor block, difficulty in wound healing, infection, necessity to remove the pump; clinical response as measured on the Ashworth and spasms scales, quality of sleep, autonomy, quality of life and pain before and after intrathecal baclofen therapy.
LE	II-2
Number of Patients and Patient Characteristics	30 patients: • Male to female ratio; 2:1 • Mean age; 51 ± 4.3 years, range (36 to 67 years) • Mean duration of symptoms; 6 years, range (1 to 3 years) Origin of spasticity: • Multiple sclerosis (73.4%) • Lateral amyotrophic sclerosis 93.3%) • Spine lesions (10%) • Spine tumours (6.7%) • Spastic paresis (3.3%) • Other (3.3%) Inclusion criteria: • Medical therapy failure • Ashworth score ≥ 3 • Spasm score ≥ 2 • Age ≥ 16 • ITB test positivity ≤ 100 µg • Severe spine deformity
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	8 months
Outcome measures/ Effect size	**Complications:** • None of the patients experienced prolonged motor block. • No local or systemic infections developed in either the immediate postoperative or the follow-up period. • Delayed surgical wound healing of the skin pocket occurred in 1 patient (3.3%), a 62 year old male diabetic patient. The wound resolved by postoperative day 14 after repeated medications and surgical toilette of the wound edges. • Catheter dislocation occurred in 1 patient (3.3%) after suddenly worsening in clinical response without rebound effect. Pump function was checked telemetrically; catheter position was reviewed radiographically. The unit was repositioned in local anaesthesia, and full clinical response was obtained. • In 1 patient (3.3%), rapid baclofen tolerance was observed after ITB implantation, but resolved after baclofen holiday. • One case of pump malfunction was observed at 4 days post implantation and resolved with replacement of the device. **Authors conclusion** The authors concluded that the good clinical response to treatment of spasticity and rigidity, improved quality of life, pain reduction and patient satisfaction with short length of admission demonstrate the efficacy of intrathecal baclofen therapy. Safe and efficacious, this mode of treatment appears to be the gold standard for treating severe spasticity.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	10. Guillaume D, Van Havenbergh A, Vloeberghs M, Vidal J, Roeste G. A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity. Arch Pys Med Rehabil. 2005;86(11):2165-2171
Study Type / Methods	Non comparative prospective cohort (pre- and post- intervention study) conducted at 24 centres in Austria, Belgium, Denmark, Germany, Luxembourg, Norway, Sapain, Sweden, Switzerland, and United Kingdom from December 1998 to December 2000. The aim of the study was to determine the impact of intrathecal baclofen (ITB) therapy on outcomes of functional independence, pain, subjective improvement, performance, and standard measures of spasticity. Clinical outcome data were collected for patients with intractable spasticity of either spinal or cerebral origin who received ITB therapy at centres in Europe. Study participants underwent a screening trial to assess their responses to ITB. Programmable pumps (Synchromed Infusion System) were implanted in patients who responded positively to the ITB trial. Spasticity in the lower and upper extremities was evaluated at entry, 3,6,9 and 12 months post implantation using Ashworth Scale assessment of muscle tone. Spasm scores was measured by Penn Spasm Frequency Scale (PSFS). Pain assessment using numeric rating scale (NRS), where patients were asked to evaluate their pain using a numeric rating (0 = no pain, to 10 = the worst pain imaginable). Motor and cognitive functions were evaluated using FIM instrument or WeeFIM for children. Patient performance and satisfaction with 1 to 5 tasks selected by themselves or their caregivers at study entry were measured on the Canadian Occupational Performance Measure (COPM). The instrument measures changes in a patient's self-perception of personal performance of specific tasks over time. Subjective ratings (very poor, poor, fair, good, very good) of overall relief from spasticity and pain with current treatments were obtained from patients and physicians at the study entry and at the 4 follow-up visits. Safety evaluations were recorded at each visit throughout the study.
LE	II-2
Number of Patients and Patient Characteristics	129 patients: • 64 % males, 36 % females • Mean age was 35.2 ± 18.8 years, range (4 to 74 years) Aetiology of spasticity (%): • Multiple sclerosis (MS) - 30% • Spinal cord injury (SCI) - 26% • Cerebral palsy (CP) - 24% • Traumatic brain injury (TBI) - 7% • Stroke (2%) • Other (11%) Inclusion criteria: Patients between 5 and 75 years of age
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Adverse events:** • After implantation, 55 (43%) reported a total of 92 adverse events over the follow-up period. • 20% of patients experienced adverse events that were patient related • 10% experienced surgery related adverse events, including cerebrospinal fluid leak (n=1), catheter dislodgement during surgery (n = 1), spinal headache (n = 1), drug adverse effect (n = 1), meningitis (n = 1), pain in left leg 9n = 1), haematoma (n = 2), incontinence (n = 2), and pocket wound infection (n =3) • 9% of patients experienced catheter related adverse events, including catheter dislodgement (n = 4), catheter kink (n = 3), catheter occlusion (n = 1), pocket seroma (n = 1), underinfusion (n = 1), and spinal headache (n = 1) • Five patients with implanted pumps died during the study but from causes considered unrelated to the study therapy • No signs and symptoms of baclofen withdrawal or overdose were reported **Authors conclusion** ITB therapy using a programmable pump is clinically effective and well tolerated, despite a seemingly high level of adverse events. In patients with intractable spasticity of spinal or cerebral origin and may offer improvements in pain relief and function.
General comments	

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Bibliographic Citation	11. Boviatsis EJ, Kouyialis AT, Korfias S, Sakas DE. Functional outcome of intrathecal baclofen administration for severe spasticity. Clinical Neurology and Neurosurgery. 2005;107:289-295
Study Type / Methods	Pre - and post- intervention study conducted at the University of Athens Medical School, Greece. The aim of the study was to estimate the functional benefit in patients with severe spasticity treated with intrathecal baclofen infusion through an implantable pump and to stress the need for functional assessment of these patients with a functional scale. Between 1999 and 2003, 22 patients with a long history of severe and disabling pharmaceutically intractable spasticity, underwent implantation of a pump for continuous intrathecal baclofen infusion. The patients were subdivided into two categories according to the aetiology of spasticity; 15 had Multiple Sclerosis and seven suffered a Spinal Cord Injury at different levels (from C4 to T11). Clinical status was assessed with Ashworth and Penn spasm scales. Functional benefits were evaluated with the Barthel index score and pain relief with a self-reported visual analogue pain scale.
LE	II-2
Number of Patients and Patient Characteristics	22 patients: • 12 males, 10 females • Average age was 44.7 years, range (27 to 63 • Average disease duration was 12.04 years (range 1 to 30 years, median 12 years). Diagnosis: • 15 had multiple sclerosis • (6 immobile, 4 wheelchair independent, 4 could walk with help) • 7 had spinal cord injury (4 paraplegic, none able to walk) Inclusion criteria: • Chronic disabling spasticity (score ≥ 4 in Ashworth scale • Failure of per oral antispastic drugs after administration of maximum tolerated or recommended doses • Duration of symptoms > 12 months • Absence of block in CSF circulation • No allergy to medication • Age < 65 years • Positive response to bolus intrathecal baclofen administration
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up of 32 months (range, 9 to 55 months, median 35 months)
Outcome measures/ Effect size	**Complications:** • Multiple sclerosis (MS) group ◦ One complication was noted. A patient presented with symptoms of baclofen CNS toxicity and muscle flaccidity 3 days postoperatively, at an infusion of 75 μg /day. The pump was immediately emptied through subcutaneous paracentesis and filled with normal saline. Laboratory test showed renal failure, treated successfully. The pump was refilled as soon as renal function returned to normal. • Spinal cord injury group ◦ One complication was noted. There was a pump explantation in a quadriplegic patient due to thinning of the skin over the device. Under local anaesthesia the pump was removed, thoroughly cleaned, disinfected and placed back in the subcutaneous pocket. This proved to be sufficient and the pump was kept in place. **Authors conclusion** Reduction of spasticity and spasms achieved with intrathecally delivered baclofen, leads to functional improvement and pain relief.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	12. Awaad Y, Tayem H, Munoz S, Ham S, Michon Am, Awaad R. Functional assessment following intrathecal baclofen therapy in children with spastic cerebral palsy. J Child Neurol. 2003;18:26-34
Study Type / Methods	Pre- and post-intervention study conducted at the Children's Hospital of Michigan, Wayne State University, School of Medicine, Detroit. The aim of the study was to describe the outcomes of a series of patients with cerebral palsy who received intrathecal baclofen to reduce spasticity. After being identified as appropriate candidates for intrathecal baclofen therapy, each patient underwent a screening trial with 50 g bolus intrathecal injection of baclofen into the lumbar region. After a positive response and pump implantation, patients were asked for follow-up assessments at 1,6,12,18 and 24 months. The patients received individualised rehabilitation, including physical and occupational therapies, speech therapy, and gait training, to maximise the functional effects of the drug. The Ashworth Scale was used as a clinical measure of impairment and the Paediatric Evaluation of Disability Inventory (PEDI) was used to assess the dimensions of functional limitations and disability. In addition groups were formed for analysis by age and level of functional mobility. Foe age, group 1 included subjects less than 18 years and group 2 consisted subjects 18 years of age or older. For functional mobility, the low mobility group consisted of subjects with baseline PEDI mobility raw scores of 0 to 15 points, and high mobility group had baseline raw scores of 21 to 54 points.
LE	II-2
Number of Patients and Patient Characteristics	39 patients: • 27 males, 12 females • Mean age was 13.69 years, SD (7.43 years), range 4 to 32 years Baseline data [Mean (SD), range]: • Ashworth scale score, = 3.25 (0.58), 2.3 to 4.8 • PEDI functional skills: mobility = 25.44 (20.41), 0 to 79.8 Inclusion criteria: • At least 4 years of age • Weigh > 30 pounds • Severe spasticity in the lower extremities (average Ashworth Scale score at least 3 in lower extremities • Undergo a trial of oral antispasmodic agent for at least 6 months
Intervention	Continuous ITB infusion and individualised rehabilitation programme
Comparison	No comparator
Length of follow up (if applicable)	24 months
Outcome measures/ Effect size	Adverse events: • Nausea (n = 4) • Constipation (n = 6) • Increased frequency of seizure (n = 2) • New onset of seizures (n = 2) – all of them had underlying brain pathology • Increased oral secretions (n = 2) • Sleepiness (n = 2) • Urinary retention (n = 1) Complications owing to the device and the surgical procedure: • Meningitis (n = 2) • Seromas (n = 7) • Pump flipped or rotated (n = 3) • Infection (n = 3) • Catheter dislocated (n = 3) • Pump was removed in 4 patients owing to adverse effects and / or lack of effect (meningitis = 1, infection = 2, and no clinical improvement n = 1) **Authors conclusion** These results provide suggestive evidence that the combination of intrathecal baclofen therapy and rehabilitation has positive effects across the dimensions of disablement.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	13. Murphy NA, Nicole Irwin MC, Hoff C. Intrathecal baclofen therapy in children with cerebral palsy: efficacy and complications. Arch Phys Med Rehabil. 2002;83:1721-1725
Study Type / Methods	Pre - and post-intervention study conducted at the University of Utah, Salt Lake City between March 1997 and Mach 2001. The aim of the study was to describe the efficacy of intrathecal baclofen (ITB) therapy in the management of spasticity in young children with cerebral palsy (CP) and to identify risk factors for complications. Candidates for ITB were identified, and each child participated in a screening trial. All 25 ITB delivery systems implanted in 23 children during the 48 month study period were reviewed. Average upper-and lower-extremity Ashworth Scale scores were assessed at baseline and after 6 and 12 months of ITB. To explore the differences between the children who required explanation of the ITB delivery system with those who did not, a series of t tests and chi-square analyses were performed.
LE	II-2
Number of Patients and Patient Characteristics	23 children with severe spasticity secondary to CP: • 17 boys, 6 girls • Age ranged from 4.5 to 17.4 years, with an average of 8.8 years and a median ± standard deviation (SD) of 7.4 ± 3.9 years. • Spastic diplegia present in 22% (5/23), Spastic quadriplegia in 61% (14/23) • Mixed-type (extrapyramidal and spastic features) in 4% (1/23), Mixed type quadriplegia in 13% (3/23)
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications:** • Explantation was required in 44% (11/25), with wound complications as the leading cause in 73% (8/11) • Complications were associated with the diagnosis of mixed-type CP, as compared with pure spastic type [explanted system, 6 whereas intact system 0 ($P \leq 0.01$)] • Trends suggest that children of smaller size and younger age, as well as those with gastrostomy tubes and non ambulatory status, were more likely to encounter complications necessitating explantation (P, non significant) **Authors conclusion** ITB therapy effectively reduced spasticity in children with CP. However, complications necessitating explantation can occur. Further research is needed to identify criteria describing the ideal paediatric candidate for ITB.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	14. Dario A, Di Stefano MG, Grossi A, Casagrande F, Bono G. Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. Acta Neurol Scand. 2002;105:83-87
Study Type / Methods	Pre- and post-intervention study conducted in Italy. The aim of the study was to evaluate long-term results of chronic intrathecal baclofen infusion on the spasticity, on the spasms and to evaluate the side-effects of the intrathecal baclofen in patients with supraspinal spasticity. Fourteen patients with severe progressive refractory to medical therapy spasticity were evaluated after chronic intrathecal baclofen infusion performed by implantation of subcutaneous pump. The patients had suffered traumatic or anoxic acquired brain injuries. The clinical evaluation was made using Ashworth Scale (AS) and the Spasm Frequency Scale (SFS). The parameters were assessed before intrathecal therapy, 3, 6, 12 hour after bolus administration of intrathecal baclofen and every 6 months after pump implantation.
LE	II-2
Number of Patients and Patient Characteristics	14 patients: • 10 males, 4 females • Mean age was 38.8 years (range; 18 to 56 years) • Glasgow Outcome Scale (GOS) score before administration of intrathecal baclofen was 2 in eight patients and 3 in six patients. • History of post injury spasticity was at least 6 months with a mean of 36.7 months
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Mean of 23.5 months after implantation (range 6 to 65 months)
Outcome measures/ Effect size	**Complications:** • One patient had a superficial wound erosion as surgical complication. • No side-effects due to intrathecal baclofen administration were observed. **Authors conclusion** The intrathecal infusion of baclofen seems to be an effective treatment in patients with supraspinal spasticity.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with for spasticity?

Bibliographic Citation	15. Dario A, Scamoni C, Bono G, Ghezzi A, Zaffaroni M. Functional improvement in patients with severe spinal spasticity treated with chronic intrathecal baclofen infusion. Functional Neurology. 2001;16:311-315
Study Type / Methods	Pre- and post-intervention study conducted in Italy. The aim of the study was to evaluate the efficacy and functional benefits of chronic intrathecal baclofen infusion in severe spinal spasticity. Twenty patients with a diagnosis of severe intractable spinal spasticity were evaluated prior to implantation of a programmable pump for chronic intrathecal baclofen therapy and at follow-up, which ranged from 12 to 36 months (mean 22.4 months). Patient assessment was based on Ashworth Scale to assess spasticity, four-point Spasm Frequency Scale to assess spasm, self-reported pain and Functional Independence Measure (FIM) scores to assess physical disability. The Wilcoxon test was used for statistical analyses.
LE	II-2
Number of Patients and Patient Characteristics	20 patients: • 9 males, 11 females • Mean age was 39.8 years (ra1ge; 27 to 52 years) • Clinical history of spasticity had a duration of at least 12 months (mean; 36.5 months) • All patients were unable to walk • Causes of spasticity: ◦ Multiple sclerosis (n = 13) ◦ Trauma (n = 4) ◦ Spinal tumours (n = 2) ◦ spinal myelitis (n =1) • All patients but 2 had spastic paraparesis
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Mean of 22.4 months after implantation (range 12 to 36 months)
Outcome measures/ Effect size	**Complications** No side-effects due to intrathecal baclofen administration were observed; one patient had a cerebrospinal fluid leak around the catheter that required surgical repair.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with for spasticity?

Bibliographic Citation	16. Korenkov AI, Niendorf WR, Darwish N, Glaeser E, Gaab MR. Continuous intrathecal infusion of balcofen in patients with spasticity caused by spinal cord injuries. Neurosurg Rev. 2002;25:228-230
Study Type / Methods	Pre- and post-intervention study conducted in Germany. The aim of the study was to determine the efficacy and safety of intrathecal baclofen therapy delivered by a programmable pump for the chronic treatment of spinal spasticity. Twelve patients with intractable spasticity caused by spinal cord injuries underwent implantation of a programmable continuous infusion pump after significant reduction in spasticity following an intrathecal test bolus of baclofen. Patients were examined 2 weeks after pump implantation and subsequently every 2 to 3 months for pump refill. The infusion rate and infusion mode were adjusted by telemetry using a briefcase-sized programmable computer. Spasticity was measured according to the degree of rigidity (Ashworth scale) and by means of a spasm frequency score in the preoperative and post-operative periods.
LE	II-2
Number of Patients and Patient Characteristics	12 male patients with spastic quadriparesis and spastic paraplegia caused by spinal cord injuries
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications:** • Complications derived from the surgical procedure and through baclofen application were rare ◦ Two cases of postoperative catheter dislocation corrected surgically ◦ No malfunctions of pumps, rupture of the catheter, or dural leak ◦ No cases of meningitis or local wound infections ◦ No respiratory depression ◦ No coma **Authors conclusion** The surgical procedure of pump and catheter implantation is simple and associated with few complications. Chronic intrathecal baclofen administered by an implanted programmable pump is a non-destructive, safe, and effective method of treatment of intractable spasticity due to spinal cord injury. The use of a programmable pump allows non invasive interrogation and programming of implanted pumps and hence a reduction in the risk of infections.
General comments	

Evidence Table : SAFETY

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Bibliographic Citation	17. Campbell WM, Ferrel A, McLaughlin JF, Grant GA, Loeser JD, Graubert C, Bjornson K. Long-term safety and efficacy of continuous intrathecal baclofen. Developmental Medicine & Child Neurology. 2002;44:660-665
Study Type / Methods	Retrospective review of a pre and post intervention study and cross-sectional survey at the Children's Hospital and Regional Medical Centre (CHRMC), Seattle, WA, USA. The aim of the study was to report on the long-term safety and efficacy of continuous intrathecal baclofen (CITB) infusion in the treatment of 21 children with intractable severe spasticity of cerebral origin. The study was based on a retrospective review of collected data in patient files and a computer database, and a prospective telephone survey. The cross-sectional survey was performed in 1999. All 21 consecutive children and adolescents who began CITB at CHRMC between December 1994 and December 1998 were included. All recipients had a successful test dose of intrathecal baclofen (50 or 100 µg) as inpatients before elective placement of the baclofen pump. Individual treatment goals were set preoperatively. The recipients were scheduled to return to the neurosurgery clinic at CHRM every 1 to 3 months for pump refill and to the Spasticity Management Clinic at 6 and 12 months after implantation where various outcomes were measured which include Ashworth scale, Gross Motor Function Measure (GMFM) and Paediatric Evaluation of Disability Inventory (PEDI). To describe more completely the benefits, adverse events, and family satisfaction with CITB, a semi-structured telephone survey was conducted for 17 recipient's stills receiving this treatment in July 1999.
LE	II-2
Number of Patients and Patient Characteristics	21 children • 15 males, 6 females • 7 had level IV severity of Gross motor Functional Classification System • 14 had level V severity of Gross motor Functional Classification System • 19 had spastic quadriplegia • 2 had spastic diplegia • All were wheelchair users • 13 had clinical athetosis or dystonia as a secondary component of their disorder
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	31 to 78 months; (mean 53 months SD; 4 months)
Outcome measures/ Effect size	**Adverse events** During 80 recipient-years of pump operation, 153 treatment-associated adverse events occurred; 27 of these were device related and 126 non-device related adverse events. • Device-related adverse events ◦ 1994-1999, 21 adverse events; 11 related to the pump / catheter system and 10 to procedural problems. Incidence of device related events was 0.48 per recipient-year of follow-up in this time segment. There were 10 surgical procedures in 7 recipients for problems related to the device. ◦ 1999-2001, 4 adverse events associated with the device related to the pump / catheter system and 2 procedure-related events (incidence of 0.17 events per recipient –year of follow–up) • Non-device-related adverse events ◦ 1994-1999, the incidence of non-device related adverse events was 2.1 per recipient-year of follow-up in this time segment. ◦ 1999-2001, the incidence of non-device related events was 0.97 events per recipient –year of follow –up) ◦ Many adverse events were referable to the CNS. Decreased function, often associated with decreased tone, was usually temporary related to the initiation of the CITB and / or increases in dose. These are often transient and reversible. ◦ All recipients who experienced seizures had known underlying seizure disorders ◦ Constipation was a frequent adverse events and required surgery in one recipient ◦ Two cases of acute pancreatitis ◦ Decubitus ulcers were reported in 10 recipients: one required hospitalisation and surgical closure ◦ Proportion of non-device related events was substantially higher in pump recipients with GMFCS level V severity in the first review period
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	18. Becker R, Alberti O, Bauer BL. Continuous intrathecal baclofen infusion in severe spasticity after traumatic or hypoxic brain injury. J Neurol.1997;244:160-166
Study Type / Methods	Pre -and post-intervention study conducted at the Philipps University Hospital, Baldingerstrasse, Marburg, Germany. The aim of the study was to report on the results in treating 18 patients with severe spasticity following traumatic or hypoxic brain injury. Eighteen patients with severe spasticity from traumatic brain injury or hypoxic brain injury were treated with continuous intrathecal baclofen infusion (CIBI). Muscle tone and spasms were assessed at admission and at discharge according to the Ashworth and Spasm frequency scores. For the assessment, the patient's highest Ashworth score was always noted. In patients 1 and 2 a significant difference in Ashworth scores between the right and left side. In these two patients the mean Ashworth score was calculated for both sides. Additional assessments, for instance of function and pain, were difficult or even impossible in these patients. Pain was assumed when patients made typical, pain associated gestures and facial movements.
LE	II-2
Number of Patients and Patient Characteristics	18 patients • 13 males • 5 females • Mean age 41 years, range (2.5 to 70 years) • 6 patients suffered from severe traumatic brain injury • 3 patients had severe multiple trauma with brain damage resulted from hypoxia • 9 patients had hypoxic brain injury • 1 patient mildly disabled, 5 severely disabled, 12 in vegetative state • 12 patients were bedridden, 6 partially mobile
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Ranges from 13 to 54 months
Outcome measures/ Effect size	**Complications** Complication rate was low: • 1 infection in pump pocket led to removal of the system • 1 patient had an epileptic seizure with the first bolus application of baclofen. It was a single event and there were no further convulsions. • In 1 patient the spinal catheter had retracted in the subcutaneous pocket, leading to a rapid loss of efficacy of CIBI. After repositioning of the catheter there were no further complications. **Authors conclusion** Further prospective clinical trials will be necessary to obtain more experience with patients suffering from supraspinal spasticity.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	19. Ochs G, Struppler A, Mehyerson BA, Linderoth B, Gybels J, Gardner BP, Teddy P, Jamous A, Weinmann P. Intrathecal baclofen for long-term treatment of spasticity: Journal of Neurology, Neurosurgery, and Psychiatry. 1989;52:933-939
Study Type / Methods	Pre- and post-intervention study conducted at four independent hospitals in four European Countries following identical investigational protocols and using the same, programmable drug-administration device (DAD) for intrathecal application of baclofen as treatment of spasticity. Strict records of adverse events, patient related and other pertinent data were collected. Many of the patients were video-recorded before and after treatment. The effect of treatment was quantified by clinical ratings, using the Ashworth-scale for muscle tone assessment and rating rates for frequency and severity of spontaneous spasms and strength of tendon reflexes. Electrophysiological measurements (EMG) recordings of motor responses were performed in a subgroup of patients to quantify the therapeutic outcome.
LE	II-2
Number of Patients and Patient Characteristics	28 patients who suffered from severe chronic para-or tetraspasticity with various aetiologies. 14 males, 14 females Mean age 46 (SD=12.2) years, range (24 to 64 years) Most confined to wheelchair or bedridden, unable to walk and dependent on continuous nursing care Most suffered from pain due to increased muscle tone or spontaneous spasms
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	24 months (2 years)
Outcome measures/ Effect size	Complications and side-effects • Complications and untoward side-effects of the procedure were few Complications: • All complications encountered in the patients were transient • 1 pump failure occurred after 3 months of normal functioning. It was caused by insufficient lubrication of the pump motor gear; this problem has been taken care of in later models and no more device failures occurred. • 1 pump had to be removed because of pocket infection 3 days after implantation and replaced 2 months later • In 2 patients the catheter had to be replaced owing to dislocation shortly after implantation Side-effects of the drug: • Some patients complained of slight fatigue or sleepiness, mainly after test bolus injection or beginning of therapy • In 2 patients concomitant self-medication, while on continuous intrathecal baclofen caused reversible coma and respiratory depression making admission to intensive care unit necessary Tolerance: • In 1 patient, a 500% increase of dose necessary. **Authors conclusion** This procedure is recommended for spasticity of spinal origin refractory to physiotherapy and oral medication. It is preferable alternative to ablative surgical intervention.
General comments	

Evidence Table : SAFETY

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Bibliographic Citation	20. Azouri P, Mane M, Thiebaut JB, Denys P, Remy-Neris O, Bussel B. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. Arch Phys med Rehabil.1996;77:35-39
Study Type / Methods	Pre- and post-intervention study conducted at a neurological rehabilitation department of a university hospital in France. The aim of the study was to assess long-term efficacy and functional benefits of intrathecal baclofen for severe spinal spasticity. Eighteen patients with severe and disabling spinal spasticity received intrathecal baclofen by an implantable pump. Patients' evaluation were done before implantation and during follow-up by spasticity measures (Ashworth scale, spasms frequency score), and by the Functional Independence Measure (FIM) `- French adaptation by P. Minaire. FIM consists of 18 items divided into 6 categories including self-care, sphincter control, mobility, locomotion, communication, and social cognition. These items are grouped into 2 fundamental subsets, one measuring motor and the second cognitive functions. Scoring on each item is based on a 7-point scale, ranging from complete independence Value = 7) to complete dependence (total assistance required = 1).
LE	II-2
Number of Patients and Patient Characteristics	18 patients who suffered from severe chronic para-or tetraspasticity with various aetiologies. • 14 males, 4 females • Average age was 38.5 years (SD = 11.6) • Average duration of disease was 8.7 years (SD = 8.7), but highly variable according to the pathology (19.5 years for multiple sclerosis (MS) patients, 5.7 for other cases) Inclusion criteria: • Severe disabling spinal spasticity (Ashworth scale score ≥ 4, spasm frequency score ≥ 3) • Ineffectiveness of oral antispastic drugs • Positive response to intrathecal baclofen
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Average follow-up was 37.4 months (range; 9 to 72 months) 10 patients were treated for more than 30 months, and 4 more than 5 years
Outcome measures/ Effect size	**Side effects** • Severe side-effects were observed in 2 patients, and were probably related to baclofen overdose. They were characterised by somnolence and muscle flaccidity. Both patients were hospitalised, one received mechanical ventilation. This patient received baclofen by a mechanical pump and probably made a mistake in pump management, which provoked an overdose. From then on, treatment was definitively withdrawn. • The other patient developed problems after a single bolus of 130 µg, without any other explanation. Treatment was continued with a lower dosage without any side effect. • In one case, a subcutaneous infection appeared under the scar shortly after implantation, and the patient recovered with simple local care. • No systemic or meningeal infection occurred. **Authors conclusion** Efficacy remained stable after 6 to 9 months. Marked improvement of functional independence was observed in paraplegic patients. Improvement was less spectacular in patients with severe upper limb dysfunction, but nevertheless appreciable in terms of life comfort and use of attendants.
General comments	

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Bibliographic Citation	21. Francisco GE, Boake C. Improvement in Walking Speed in poststroke spastic hemiplegia after intrathecal baclofen therapy: A preliminary study. Arch Phys Med Rehabil. 2003;84: 1194-1198
Study Type / Methods	Pre- and post-intervention study conducted at a tertiary care centre, Houston, Texas, USA. The aim of the study was to explore whether intrathecal baclofen (ITB) therapy improves ambulation in stroke survivors. Participants were from the spastic hypertonia clinic of a freestanding rehabilitation hospital over a period from late 1998 to 2001. Participants underwent a screening procedure to determine responsiveness to ITB. The ITB pump for continuous infusion was implanted with the patient under general anaesthesia. The 4 outcome measures were assessed before and after pump implantation. The 4 outcome measures include customary walking speed which was calculated for the time it took a participant to walk 50 ft (15 m), with or without assistance, on a level surface at a self-comfortable pace, functional walking category, Modified Ashworth scale and Functional Mobility Score. Five items were rated to reflect functional mobility skills; locomotion-walking and stairs item of FIM instrument, the community access item of the FAM, and 2 unpublished item (Sit - stand, Stand - Sit).
LE	II-2
Number of Patients and Patient Characteristics	10 adults with poststroke hemiparesis who were ambulatory at the time of pump implantation. • 5 males, • 5 females • Mean age was 51.7 years • Mean time interval from stroke onset to pump implantation was 28.6 months (median ± SD, 24 ± 15.8 months; range; 9 to 55 months) Inclusion criteria: • Spasticity resulting from stroke • MAS score ≥ 2 in at least 2 limbs • Age ≥ 18 years • Inadequate spasticity control with other pharmacologic and physical modalities • No known allergy to baclofen • Ambulatory at any level of assistance before pump implantation
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean time interval from pump implantation to follow-up 8.9 months (median, 7 ± 6.1 months; range, 4 to 25 months)
Outcome measures/ Effect size	**Adverse events** Each of the following events were reported by 2 participants; headache, nausea, vomiting, excessive weakness, and transient urinary retention Another participant had urinary retention and was later found on urodynamic studies to have a flaccid bladder requiring suprapubic tube placement. He elected to have the tube placed rather than to discontinue ITB therapy, because of the improvement in spasms and muscle tightness **Authors conclusion** This preliminary study suggests that ITB therapy, in combination with physical therapy, may improve walking speed and functional mobility in ambulatory individuals with poststroke spastic hemiplegia.
General comments	Industry sponsored

Evidence Table : SAFETY

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Bibliographic Citation	22. Mota F, Stignani C, Antonello CE. Upper limb function after intrathecal baclofen treatment in children with cerebral palsy. J Padiatr Orthp. 2008;28(1):91-96
Study Type / Methods	Pre-and post-intervention study conducted at the Paediatric Orthopaedics Department of "V. Buzzi" Children's Hospital, Milan, Italy. The aim of the study was to evaluate the motor function of the upper limbs in patients with cerebral palsy (CP) treated with ITB. A consecutive series of 20 patients with spastic CP aged between 5 and 15 years and able to understand the required tasks from the Melbourne scale implanted with pumps was studied. The patients were followed up over 12 month period for assessment of the upper limb function with the Melbourne Assessment of Unilateral Upper Limb Function scale, an assessment protocol that measures the quality of upper limb function in children between the ages 5 and 16 years with neurological impairment. The tool is composed of 16 items with a maximum score of 122. The patient performance is video recorded and to assign a score after the test is completed. At every follow-up, the patients were also administered a subjective questionnaire for internal use that investigated the aspects of patient's life through 26 questions. Degree of satisfaction with the treatment was investigated through 2 questions.
LE	II-2
Number of Patients and Patient Characteristics	20 patients • 15 boys • 5 girls • Average ◦ Age range at the time of implantation was 11.4 years (SD, 3.57 years, range 5 to 15 years ◦ 9 patients had spastic diplegia, 11 had quadriplegia ◦ All 20 patients were classified between levels II and V of the Gross Motor Function Classification System (GMFCS) ◦ 2 patients GMFCS level II, 8 patients GMFCS level III, 7 level IV, 3 level V
Intervention	Continuous ITB infusion. Programmable pump device (Medtronic, Minneapolis, Minnesota)
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications** • Complications related to catheter occurred in 3 of 20 patients in the study. In 2 cases the catheter ruptured, and in 1 case, it came out. In all 3 patients, the catheter was replaced. • No complications related to drug have been reported during the study period. **Authors conclusion** The subjects with CP of different degrees of severity had an improvement in quality of the upper limb function and showed overall satisfaction with the results achieved. The study also shows the importance of evaluating the quality of upper limb function in children with CP treated with ITB therapy
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	23. Burns AS, Meythaler JM. Intrathecal baclofen in tetraplegia of spinal origin: efficacy for upper extremity hypertonia. spinal Cord. 2001;39:413-419
Study Type / Methods	Pre- and post -intervention study conducted at the University of Alabama at Birmingham, Alabama, USA. The aim of the study was to evaluate the efficacy of intrathecal baclofen (ITB) for upper extremity spastic hypertonia in tetraplegia of spinal origin. The medical records of 14 individuals with tetraplegia of spinal origin who underwent intrathecal baclofen pump placement were reviewed. The effects of intrathecal baclofen on spasm frequency, deep tendon reflexes, and tone (Ashworth scale) were assessed for the upper and lower extremities for a 1 year follow-up period.
LE	II-2
Number of Patients and Patient Characteristics	14 patients with spinal cord pathology afflicting the cervical segments (C1 – T1) • All study subjects had sustained their injuries at least 6 months prior to baclofen pump placement and failed to response to oral agents • 12 males • 2 females • Age range (25 to 64 years)
Intervention	Continuous ITB infusion. Programmable pump device
Comparison	No comparator
Length of follow up (if applicable)	12 months (1 year)
Outcome measures/ Effect size	**Complications** • Pump placement was well tolerated by all patients and there was no significant complications during the 12 month follow-up period • There were no reported cognitive side effects, related seizure breakthroughs or changes in urinary or faecal voiding patterns • One patient develop a pocket infection approximately 20 months after pump placement and necessitated surgical replacement, however this occurred outside the 1 year study follow-up period **Authors conclusion** ITB is a safe and effective intervention in treating upper extremity hypertonia of spinal origin.
General comments	Retrospective

Evidence Table : SAFETY
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Bibliographic Citation	24. Krach LE, Nettleton A, Klempka B. Satisfaction of individuals treated long-term with continuous infusion of intrathecal baclofen by implanted programmable pump. Paediatric Rehabilitation. 2006;9(3):210-218
Study Type / Methods	Cross sectional study conducted at a regional specialty hospital for children and young adults with disabilities at the Gillette Children's Specialty Healthcare, St. Paul, USA. The aim of the study was to investigate the perspective of the individual receiving intrathecal baclofen (ITB) or his / her caregiver concerning effects and to describe characteristics of those that were satisfied or not satisfied. After IRB approval, potential subjects were identified who had undergone ITB pump implantation at least 1 year prior to the study. In order to be considered for the use of intrathecal baclofen at the institution, individuals must have an average Ashworth score of 3 or more in the lower extremities. One hundred subjects / caregivers were interviewed by phone. Interview consisted of a scripted questionnaire to obtain subject / caregiver opinions about changes in function and caregiver assistance, as well as satisfaction with ITB. Medical records were reviewed to collect information including diagnosis, ITB related surgeries and medications. Ratings / changes were classified as much better, somewhat better, no change, somewhat worse, much worse, and not applicable.
LE	II-3
Number of Patients and Patient Characteristics	100 subjects: Those who answered the survey included: • Mother of subject (59) • Father of subject (17) • self (10) • Nurse or other caregiver (9) • Foster mother (4) • Grandmother (3) • Grandfather (1) • Subjects ranged from 5 to 42 years of age, with a mean of 15 years. • 88 had Cerebral palsy • Mean time from pump implantation to interview was 2.6 years with a range of 1-3.75 years • All subjects had spasticity • 59 males, 41 females
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up duration was 31.9 months
Outcome measures/ Effect size	**Events related to ITB hardware or surgery** 22 subjects experienced 32 events related to the ITB hardware or surgery. This included catheter obstruction, migration or fracture (12 events), post-operative infection and explants with subsequent re implantation (6 events), catheter pump connector tear (7 events), catheter tip repositioning (1 event). Six pumps were replaced for low battery. **Authors conclusion** Generally, subjects and their caregivers were satisfied with the results after ITB pump implantation. A majority reported improvements in positioning, transfers, dressing, toileting / hygiene and comfort.
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	25. Brochard S, Remy-Neris O, Filipetti P, Bussel B. Intrathecal baclofen infusion for ambulant children with cerebral palsy. Pediatr Neurol. 2009;40: 265-270
Study Type / Methods	Pre- and post-intervention study conducted at six rehabilitation departments in France. The aim of the study was to assess the effects of continuous intrathecal infusion of baclofen on the gait of ambulant children with cerebral palsy. The study involved a retrospective, consecutive case series of children and young adults who had received intrathecal baclofen infusions. Data were collected for each participant at the time of intrathecal baclofen pump implantation and during the last follow-up visit when a change in dose delivery was effected. Details collected included Gillette Functional Assessment Questionnaire score, use of walking aids, Ashworth Scale score, and joint angle at which the stretch reflex was triggered.
LE	II-2
Number of Patients and Patient Characteristics	21 ambulant children and young adults with cerebral palsy • 12 diplegic children, 8 quadriplegic children, 1 triplegic child • 14 girls • 7 boys • Mean age of 11 years and 10 months (SD, 4 years and 10 months; range, 6 to 22 months) • Gross Motor Function Classification – 17 as level III, 4 as level II • Median initial Gillette Functional Assessment Questionnaire score was 5 (SD,2: range, 2 to 9) • Most of the children had a crouch gait pattern (n = 10) or true equines (n = 8) Inclusion criteria: • Primary diagnosis of cerebral palsy • Able to walk with or without an assistive device at least in physiotherapy
Intervention	Continuous ITB infusion. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Mean duration of treatment was 25.8 months (range, 5 to 57 months)
Outcome measures/ Effect size	**Complications** • After implantation 1 patient developed aseptic meningitis • During follow-up period, 3 catheter ruptures, 3 catheter migrations, and 1 meningocele required further surgical procedures • 1 child developed cutaneous necrosis and required permanent removal of the pump • Overall, nine patients out of 21 underwent further surgery, such as catheter reimplantation or pump removal **Authors conclusion** Continuous intrathecal baclofen appears to decrease spasticity and improved the gait capacity of children with cerebral palsy.
General comments	Retrospective

Evidence Table : SAFETY
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Bibliographic Citation	26. Sadiq AS, Wang GC. Long-term intrathecal baclofen therapy in ambulatory patients with spasticity. J Neurol. 2006;253:563-569
Study Type / Methods	Pre- and post-intervention study conducted at the MS Research and Treatment Centre of New York, Albert Einstein College of Medicine, New York, USA. The aim of the study was to determine the effects of ITB on ambulatory patients with spasticity with particular attention to functional outcomes and ambulation. Patients considered for ITB therapy included those with: 1) moderate to severe spasticity with Ashworth score of ≥ 3 in the most severely affected muscle, 2) intolerance or sub-optimal response to oral anti-spastic agents, 3) relatively intact muscle strength, 4) stable or optimally managed underlying neurological disease.Thirty six patients with severe spasticity previously screened for response to ITB were implanted with programmable pumps that allowed for continuous infusion of ITB. Patients were followed after implantation from 1 to 13 years. Quality of Life (QOL) measure for ambulatory function: All patients self-reported on a modified version of the 12-Item MS walking Scale (MSWS-120. The patients recorded their responses on a baseline and at 6 months post-implant. The MSWS-12 was modified by substituting the effect of MS to the effect of pump implantation on 12 measures of ambulatory function.
LE	II-2
Number of Patients and Patient Characteristics	36 adult ambulatory patients with spasticity Ambulation was defined as the ability to walk at least 25 feet with or without the use of an assisted device • 19 males • 17 females • Age at initial pump implantation ranged from 19 to 66 years • 27 had multiple sclerosis (MS) • 1 had primary lateral sclerosis (PLS) • 2 had spinal cord injury (SCI) • 6 had other neurological disorders • 31 of 36 patients had spinal spasticity • 5 were hemiparetic
Intervention	Continuous ITB infusion. Medtronic programmable pump
Comparison	No comparator
Length of follow up (if applicable)	1 to 13 years
Outcome measures/ Effect size	**Complications** • 15 patients had their pumps replaced: 10 had low battery alarms after 4 to 5 years, the remaining 5 patients needed catheter replacement and the pumps were replaced if more than 3 years had elapsed following initial implant • The most common complication has been catheter problems, which occurred in 8 patients (all required replacement of their catheters) • 3 of the 36 patients had unique complications: 1 had pump-site discomfort, 1 developed a cystic swelling around the pump, 1 developed a pseudomeningocele **Authors conclusion** ITB therapy may be used in selected ambulatory patients with spasticity and is not associated with loss of ambulatory function.
General comments	Retrospective

Evidence Table : SAFETY
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Bibliographic Citation	27. Gooch JL, Oberg WA, Grams B, Ward LA, Walker ML. Complications of intrathecal baclofen pumps in children. Pediatr Neurosurg. 2003;39:1-6
Study Type / Methods	Pre- and post-intervention study conducted at Salt Lake City, Utah, USA. The aim of the study was to describe the complications in 100 consecutively treated children and young adults who received intrathecal baclofen pumps for the management of severe spasticity. Between January 1997 and June 2002, 100 patients under the age of 22 years had 117 intrathecal baclofen pumps surgically implanted for the management of severe spasticity. The pumps implanted were all Medtronic Synchromed Pumps (Medtronic Inc., Minneapolis, Minn., USA. Sixty one pumps had catheter ports while 56 did not. Fifty pumps had 1-piece catheters and 67 had 2-piece catheters. All patients underwent trial injections of intrathecal baclofen before pump implantation. All patients responded to the trail injections with significant reductions of muscle tone. Chart reviews were performed to document complications. The cut off date for complications was July 15, 2002. The complications included were device related complications and pronounced physiologic reactions to the drug. The frequency of the most common device related complications was examined with respect to pump type and catheter type.
LE	II-2
Number of Patients and Patient Characteristics	100 patients • Youngest patient was 3.7 years and oldest was 21 years at the time of pump placement • Average age was 11.2 years
Intervention	Continuous ITB infusion. Medtronic Synchromed Pumps (Medtronic Inc., Minneapolis, Minn., USA)
Comparison	No comparator
Length of follow up (if applicable)	Ranged from 6 months to 5.6 years
Outcome measures/ Effect size	**Complications** • 24 patients (24%) had a total of 48 complications • Several patients had more than 1 complication (5 patients had 2 complications, 6 had 3 complications, 1 had 4 complications and 1 had 5 complications) • Device related complications were: catheter disconnection(11 cases - 9% of pump implanted), catheter dislodgement (10 cases – 8% of pump implanted), pump infection (5), CSF leak [persistent] (4), catheter kink (4), catheter tear (3), catheter access port defect (2), pump flipped (2), CSF leak with infection (1), Baclofen pump failure (1) • Catheter disconnection occurred more frequently in pumps with catheter access ports (16%) than in those without ports (2%) • Minimum number of days until detection of first device related complication was 7 days and the maximum was 807 days, with an average of 262 days • Non device related complications were: mental status decline (2 cases), bradycardia (1), severe spasms (1), overdose (1) • Patient and family education is critical in preventing serious consequences of baclofen withdrawal resulting from catheter related complications
General comments	

Evidence Table : SAFETY
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Bibliographic Citation	28. Borowski A, Littleton AG, Borkhuu B, Presedo A, Shah S, Dabney KW, Lyons S, McMannus M, Miller F. Complications of intrathecal baclofen pump therapy in pediatric patients. J Pediatr Orthop. 2010;30(1):76-81
Study Type / Methods	Pre- and post-intervention study conducted at the Alfred 1. du.Pont Hospital for Children Poland. The aim of the study was to investigate and evaluate complications related to ITB treatment in children with cerebral palsy and report the subjective opinions of parents /caregivers of these children. Reviewed consecutive series of paediatric patients treated with ITB between 1997 and 2006 at the hospital. During follow-up, 8 deaths occurred with no evidence of pump or catheter malfunction in any way contributing to the cause of death. Acute infection within 60 days of the surgery and late infection rates were calculated on the basis of number of incidents /follow-up patient years, respectively. Independently, a blinded caregiver phone questionnaire was completed in 92 cases.
LE	II-2
Number of Patients and Patient Characteristics	174 patients with diagnosis of cerebral palsy (8 with mixed dystonia and 2 with mixed athetosis), and 3 were diagnosed with pure dystonia. • 71 females, 103 males • Average age at initial implant was 12 years
Intervention	Continuous ITB infusion. SynchroMed, Medtronic programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Average follow-up was 3 years, 2 months (SD=2 years, 4 months)
Outcome measures/ Effect size	**Complications** • 78 procedures in 57 patients related to complications • 54 of 174 patients (31%) had a complication requiring surgical treatment over a 3-year follow-up period • Device related complications represent 12.3% (39/316) of all performed procedures: 4 pump replacements for acute pump failures, 9 catheter replacements for catheter breaks, 7 catheter revisions for catheter disconnections, and 16 catheter replacements for catheter malfunction. There were 3 pump revisions for pump hyperrmobility. • Acute infection rate was 4.0% • The probability of developing a late infection was 1.0% per year of follow-up **Satisfaction with treatment** On the basis of follow-up questionnaire, 81% of parents / caregivers were satisfied with the treatment, and 87% would recommend ITB therapy **Authors conclusion** ITB therapy is a safe and effective treatment for severe spasticity in the paediatric population, but does have a 31% rate of complications requiring surgical management over a 3-year treatment period. Parents and caregivers have a high rate of satisfaction and would recommend the treatment to others.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with for spasticity?

Bibliographic Citation	29. Wunderlich CA, Krach LE. Gram-negative meningitis and infections in individuals treated with intrathecal baclofen for spasticity: a retrospective study. Developmental Medicine & Child Neurology. 2006;48:450-455
Study Type / Methods	Cross sectional study conducted at Gillette Children's Specialty Healthcare, a regional children's specialty medical centre located in St Paul, MN, USA. The aim of the study was to describe signs, symptoms, and clinical outcomes of individuals undergoing intrathecal baclofen (ITB) therapy who experienced pump-related Gram-negative infections including meningitis. Inclusion criteria were:1) increased muscle tone requiring ITB, 2) evidence of Gram-negative infection or meningitis by laboratory culture involving the ITB system. After identification of patients through the office of infection control, patients' charts were reviewed for relevant factors in Gram-negative infections and meningitis to determine clinical patterns, outcomes, and potential optimal treatments and / or managements.
LE	II-3
Number of Patients and Patient Characteristics	12 individuals with Gram negative infections • 9 males, 3 females • Mean age was 17 years 9 months (SD, 6.89), range; 10 to 32 years • 9 had spastic quadriplegic, 3 had spastic quadriparesis
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Complications** • A total of 571 baclofen pump surgeries were performed from 1996 to 2003, with 45 infections. Of the 45 total infections noted in the chart review, 12 were Gram-negative infections. Only 2 of these 12 Gram-negative infections resulted in meningitis; the other 10 were combinations of pocket, back wound and skin infections. • 10 of 12 Gram-negative infections (21 site encounters) occurred within 60 days of surgery. • 11 of 12 pumps were explanted • By site encounters, Pseudomonas aeruginosa accounted for 8 Gram-negative infections, Escherichia coli for 5, Proteus for 3, Enterobacter cloacae for 2, and Klebsiella, Enterobactor aerogenes, and Enterobactor vulnaris for one each • 2 individuals with Gram-negative meningitis were admitted 72 to 96 hours after hospital discharge following pump replacement. Both patients had a rapid deterioration requiring transfer to the paediatric intensive care unit, and developed coagulopathy and decrease in responsiveness. Both have improved and have elected not to replace the ITB pump.
General comments	

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Bibliographic Citation	30. Taira T, Ueta T, Katayama Y, Kimizuka M, Nemoto A, Mizusawa H, Liu M, Koito M, Hiro Y, Tanabe H. Rate of complications among the recipients of intrathecal baclofen pump in Japan: A multicentre study. Neuromodulation.2013;16:26-272
Study Type / Methods	Cross sectional study conducted at multicentres in Japan. The aim of the study was to evaluate the incidence of complications of intrathecal baclofen (ITB) therapy for spasticity in Japan, where a unique training course and nationwide registration are required. An analysis of complication was performed in all patients who underwent ITB in Japan from 2005 to 2011. Prior to surgery, all the doctors involved took a one day training course, which included hands-on training. Surgical techniques that avoided complications were emphasised.
LE	II-3
Number of Patients and Patient Characteristics	400 patients having severe spasticity • 277 men, 123 women • Average age was 47.2 + (SD, 19 years) • 223 had spasticity of spinal origin, 171 had spasticity with cerebral origin, 6 had both spinal and cerebral origins • 144 had paraparesis, 201 had tetraparesis, 41 had hemiparesis
Intervention	Continuous ITB infusion. Medtronic Model 8711 (Medtronic Inc., Minneapolis, MN, USA)
Comparison	No comparator
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**Complications** • A total of 406 pumps were implanted in 400 patients having severe spasticity. Because the study is currently in progress, among the 400 patients, 78.3% (313/400) had finished a one year follow-up. • All cause adverse events were seen in 148 patients (37%), and 93 (23.3%) of these were regarded as severe. • Catheter problems were observed in 34 (8.5%) patients: catheter migration in 25 (6.3%), breakage in 6 (1.5%), obstruction in 2 (0.5%), kinking in 1 (0.3%), and dislodgement in 1 (0.3%). • Pump trouble was observed in 7 (1.8%) patients: alarm abnormality in 1 (0.3%), memory error in 1 (0.3%), delayed recovery in 1 (0.3%), rotation in 1 (0.3%), malfunction in 1(0.3%), and abnormal infusion rate in 2(0.6%). • Device related and surgical wound infection occurred in 12 patients (3%), and 9 were regarded as severe. • Leakage or subcutaneous accumulation of cerebrospinal fluid was seen in 13 patients (3.3%) **Authors conclusion** The requirement of taking training course before starting ITB seemed to reduce complications. Although there were surgery related complications, the rate of complications in Japan appeared to be lower than those reported in larger series of ITB. However, whether the reported rates can be ascribed to a mandatory training course requires further investigations.
General comments	

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Bibliographic Citation	31. Fjelstad AB, Hommelstad J, Sorteberg A. Infections related to intrathecal baclofen therapy in children and adults: frequency and risk factors. J Neurosurg Pediatrics. 2009;4:487-493
Study Type / Methods	Cross sectional study conducted at the National Hospital, Rikshospitalet, Oslo. The aim of the study was to determine the frequency of infection and to identify risk factors for infection in connection with the implantation of an intrathecal baclofen (ITB) pump. This retrospective study included all paediatric and adult patients who received ITB at Rikshospitalet during the years 1999-2005. A database was created that included the following variables: patient age, sex, weight, diagnosis, surgical procedure performed, presence of percutaneous endoscopic gastrostomy (PEG) tube, urinary as well as faecal incontinence, anaesthetist's classification of patient status (American Society of Anaesthesiologists grade), timing of antibiotic administration, surgeon, assisting nurse, and surgical procedure time. Moreover, the mode of intrathecal screening trial (transcutaneous versus subcutaneous catheter insertion) and any complications were registered. The authors differentiated between deep and superficial infection, and they registered the causative agent.
LE	II-3
Number of Patients and Patient Characteristics	163 patients • 101 male, 62 female • 91 were paediatric patients, whose median age at study entry was 10 years (range 2 to 17 years) • 72 were adults whose median age at study entry was 44 years (range 18 to 70 years)
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months from the date of implantation
Outcome measures/ Effect size	**Complications** • A total of 408 surgical procedures were performed. • When a pump was implanted subsequent to a screening trial with transcutaneous catheter insertion, the rate of infection was 9% in the paediatric patients. The corresponding infection rate for pumps implanted after a screening trial with a subcutaneous distal catheter (Albright Method) was 12%. This difference was not significant. • Significantly higher incidence deep infections following pump implantation in the paediatric group (10%) than in the adult group (0%), P = 0.028. • Presence of PEG tube increased the incidence of infection (P = 0.008) and may be one of the main reasons for a higher frequency of infection in children. • When the patient suffered urinary and / or faecal incontinence, there was a higher chance of infection (P = 0.021). • Most common causative agent was Staphylococcus aureus, responsible for 69% of deep infections. • 69% of deep infections occurred within 1 month after surgery. **Authors conclusion** Rate of infection is significantly higher in children undergoing ITB pump implantation than it is in adult. Screening trials applying the Albright method fail to reduce the frequency of infection subsequent to pump implantation. The presence of PEG tube has the greatest significance as a predictor of infection.
General comments	

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Bibliographic Citation	32. Buonaguro V, Scelsa B, Curci D, Monforte S, Iuorno T, Motta F. Epilepsy and intrathecal baclofen therapy in children with cerebral palsy. Pediatr Neurol.2005;33:110-113
Study Type / Methods	Pre- and post-intervention study with control group conducted at the Children's Hospital V. Buzzi, Milan, Italy. The aim of the study was to analyse the relationship between epilepsy and intrathecal baclofen therapy. A retrospective study before-after trial with a consecutive sample of 150 children with cerebral palsy or spasticity of cerebral origin operated on intrathecal baclofen was conducted. A control group of 100 children with cerebral palsy, operated on other procedures at the same time, was also considered to evaluate the prevalence of epilepsy before surgery. The data, obtained at enrolment and during follow-up included age, neurologic examination, baclofen dosage, Ashworth scale, presence of clonus, and spasms. History and description of seizures, if any, were reviewed from the patient diaries and from interviews with parents. After pump implantation, duration and change in seizure frequency of focal seizures and secondarily generalise seizures were determined. Worsening was defined as the increase in seizure of more than 30% of overall seizures; improvement was defined as a decrease in seizure frequency of 50% or more. Children with values in seizure frequency between these limits were considered unchanged.
LE	II-2
Number of Patients and Patient Characteristics	Study group (ITB); 150 children • 70% of children quadriplegic, 15.4% had spastic-dyskinetic, 12.6% diplegic, 2% hemiplegic Control group; 100 children • 52% quadriplegic, 32% diplegic, 8% mixed cerebral palsy, 6% hemiplegic
Intervention	Continuous ITB infusion
Comparison	Not treated with continuous ITB infusion
Length of follow up (if applicable)	Mean follow-up was 39.27 months (SD, 17.3 month, range 6 to 65 months)s
Outcome measures/ Effect size	**Epileptic seizures** • In the study group; 60 of 150 children (40%) with epilepsy before intrathecal baclofen, 90 of 150 children (60%) without epilepsy • In the control group; 37% of children with epilepsy and 63% without it (odds ratio between intrathecal baclofen and control group regarding epilepsy; 1.13, 95% confidence interval (CI): 0.67 to 1.91 • 8 of 60 children (13.3%) with prior epilepsy manifested an improvement after intrathecal baclofen in seizure frequency, whereas, 2 children worsened and 1 child had seizures ex novo • 4 of 8 patients experienced seizure remission and discontinuation of antiepileptic treatment • No significant difference were evident among children who improved or worsened regarding sex, Ashworth scale, clonus, and spasms **Authors conclusion** In children with spasticity of cerebral origin, intrathecal baclofen does not seem to aggravate or induce seizure activity.
General comments	Retrospective

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Bibliographic Citation	33. Schuele SU, Kellinghaus C, Shook SJ, Boulis N, Bethoux FA, Loddenkemper T. Incidence of seizures in patients with multiple sclerosis treated with intrathecal baclofen. Neurology. 2005;64:1086-1087
Study Type / Methods	Pre- and post-intervention study with matched control at Cleveland Clinic Foundation, Cleveland. The aim of the study was to assess the prevalence of epilepsy in a cohort of patients with long-standing multiple sclerosis (MS) and the potential effect of ITB on seizure frequency. Also compared the incidence of newly occurring seizures in a group of patients with MS treated with ITB with that of matched controlled group. Data were obtained from the Cleveland Clinic MS Centre ITB Therapy Registry. All patients with definite MS who underwent implantation of an ITB pump from 1990 to 2002 were included. Patients were selected for ITB pump implantation if they had severe lower extremity spasticity, failed oral spasticity medications, and had a positive response to a test injection of ITB. MS severity was determined by the Expanded Disability Status Scale (EDSS). Patients with MS not treated with ITB were matched by age, gender, and disease severity and then observed for the same period as the patients on ITB. Both patients were seen regularly in the outpatient clinic every 3 to 6 months. The prevalence of epilepsy and frequency of seizures before pump implantation and the incidence of new seizures were determined by retrospective chart review.
LE	II-2
Number of Patients and Patient Characteristics	ITB group; • 99 patients: • 68 females • 31 females • Age, 49 ± 7 years • Disease duration, 19 ± 9 years • EDSS, 7.4 • Epilepsy, 4 preexisting Control group; 99 patients: • 79 females • 21 females • Age, 50 ± 10 years • Disease duration, 17 ± 9 years • EDSS, 7.4 • Epilepsy, 5 preexisting
Intervention	Continuous ITB infusion
Comparison	Not treated with continuous ITB infusion
Length of follow up (if applicable)	3 years ± 2.6 years after baclofen pump implantation
Outcome measures/ Effect size	Epileptic seizures • Seizure frequency was less than once per year, and no noticeable change in seizure frequency was detected after initiation of ITB therapy • During the observation period, new onset of epileptic seizures was seen in 7 patients in the ITB group and in 1 patient in the control group, $P < 0.05$ • Among 7 patients with new seizures in the ITB group, 5 patients had a single event, all associated with additional aggravating factors: febrile illness, accidental baclofen overdose, serum sodium of 124 mmol/L, and post- operative setting. Two patients developed recurrent seizures, both with more than 3 seizures per year and in 1 associated with recurrent febrile urinary tract infections. • 2 patients developed single episodes of nonconvulsive status epilepticus (NCSE), and one demonstrated recurrent focal motor status epilepticus after initiation of ITB therapy. The 1st patient developed NCSE immediately after baclofen pump implantation due to accidental overdose of 10-fold and the 2nd patient developed NCSE in the setting of sepsis 3 months after pump implantation. The 3rd patient developed recurrent focal motor status epilepticus 2.5 years after ITB therapy, repeatedly occurred in the setting of febrile urinary tract infections and resolved with antibiotics and antiepileptic therapy while ITB treatment was continued.
General comments	

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Bibliographic Citation	34. Castano B, Benito J, Ferreira S, Lopez R, Vidal J. Delirium secondary to intrathecal baclofen. Spinal cord. 2009;47:477-480
Study Type / Methods	Case control retrospective study at Spinal cord injury unit in Barcelona, Spain. The aim of the study was to describe the psychiatric manifestations due to intoxication or withdrawal of ITB and to explore possible risk factors for the presentation of delirium secondary to baclofen. Selected patients who presented with delirium related to baclofen treatment. Filtered these cases by search of key words. All the compatible episodes were then reviewed and positive cases were confirmed to perform a descriptive analysis of the different variables. To study differences between the patients who presented confusional state and those who did not, 12 control patients were randomly selected from the total ITB population studied without a history of delirium, intoxication or withdrawal from baclofen. Patients were homogenous for age, sex, injury level, time of implantation of the pump and baclofen dose.
LE	II-2
Number of Patients and Patient Characteristics	Patients with delirium; 12 patients: • 83.3% females • Mean age, 51 years (SD, 14.1) • Aetiology, 83.3% traumatic • Depression, 58.3% • Overmedication > 9 drugs, 0 • Psychoactive medication, 41.7% • Cognitive impairment, 33.3% • Baclofen dose, 266 µg/ day Patients without delirium; 12 patients: • 83.3% females • Mean age, 38.5 years (SD, 15.9) • Aetiology, 50.0% traumatic • Depression, 33.3% • Overmedication > 9 drugs, 8.3% • Psychoactive medication, 41.7% • Cognitive impairment, 8.3% • Baclofen dose, 222 µg/ day
Intervention	Continuous ITB infusion Medronic Synchromed infusion pump system
Comparison	No comparator
Length of follow up (if applicable)	Between 1 and 14 years
Outcome measures/ Effect size	Delirium • Frequency of delirium secondary to ITB was 9.5% (12/126 patients) in the 14 years of follow-up, eight cases (66.6%) due to intoxication and 4 (33.3%) due to withdrawal • A total of 3 (25%) of 12 patients with delirium had a fever at the time of the onset of the psychiatric symptoms • No fatal cases due to delirium • Intoxication symptoms coincided with the first filling of the pumps in 4 patients, after pump refill in 2 patients, and after a dose increase during a refill in 2 patients • Withdrawal causes were due to empty pump reservoir in 2 cases and end of battery life in 2 cases • Average time from pump implantation to the presentation of the intoxication symptoms was 8 months (from day 1 to 4.5 years), while the average time from pump implantation to the presentation of withdrawal symptoms was 7.4 years (from 4.9 to 9.9 years), P = 0.016 • Psychiatric manifestations were present for 1-3 days in 75% of the patients with delirium. In the intoxication group, symptoms did not persist beyond the third day and roughly 25% of these patients had symptoms for less than 24 hours. This findings were opposite of those in patients with withdrawal. In this group, no patients had symptoms less than 24 hours and 25% of patients presented symptoms for more than 3 days. • The therapeutic interventions used consisted mainly of modifications of the ITB dose and supportive measures
General comments	

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Bibliographic Citation	35. Heetla HW, Staal MJ, Kliphuis C, van Laar T. The incidence and management of tolerance in intrathecal baclofen therapy. Spinal cord. 2009;47:751-756
Study Type / Methods	Retrospective long term follow-up study at the University medical Centre Groningen, Netherlands. The aim of the study was to study the incidence and management of tolerance in patients treated with intrathecal baclofen (ITB) therapy. All patients treated with ITB at the departments of neurology and neurosurgery of the University Medical Centre Groningen from 1991 to 2005 were screened for the study. The patient needed at least a follow-up of 1 year to be included. After implantation all patients were treated with simple continuous ITB infusion. Tolerance in this study was defined as a yearly increase of at least 100 µg baclofen to maintain a stable spasmolytic effect. If patients showed tolerance they were offered 3 treatment options: switch to complex continuous infusion, switch to pulsatile bolus infusion, or drug holiday. The effects of treatment changes were analysed. Patients showing tolerance were compared to the non tolerant patients.
LE	II-3
Number of Patients and Patient Characteristics	37 patients with spasticity treated ITB therapy: • 19 males • 18 females Indication for ITB treatment was severe spasticity due to: multiple sclerosis (14 patients), traumatic spinal cord injury (SCI) in 10 patients, miscellaneous causes (13 patients)
Intervention	Continuous ITB infusion , Programmable pump (Synchromed I(a) or II(a), Medtronic Inc).
Comparison	No comparator
Length of follow up (if applicable)	Between 3 to 120 months, mean of 38 months
Outcome measures/ Effect size	**Tolerance** Dose titration of ITB: • Mean dose increased significantly ($P < 0.05$) during the first 18 months and stabilised afterwards at 350 µg • 8 patients (22%) developed tolerance, defined as dose increase of > 100 µg per year • No predictive factors for the development tolerance could be determined Strategies to treat tolerance: • Altering the infusion mode from simple to complex continuous (n = 6) had no effect on the development of tolerance • Pulsatile bolus infusion (n = 1) and drug holiday (n = 20) were both effective in reducing the daily baclofen dose Influence of pump / catheter revisions on the dose of baclofen: • Patients who needed surgical revision of the pump system because of mechanical failures (n =11) showed significant dose decrease during the first month after revision, indicating that the preoperative dose increase most likely had been caused by pump failure • Pump related complications occurred once per 10.5 years of ITB treatment Drug related side effects: • Annual risk of 13.8% • Reported events mostly mild (drowsiness, swallowing difficulties, decubitus, urine incontinence and auditory hallucinations were reported most frequently) **Authors conclusion** ITB therapy is effective and safe, also in the long term and causes tolerance in only 22% of the treated patients
General comments	

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Bibliographic Citation	36. Ginsburg GM, Lauder AJ, Progression of scoliosis in patients with spastic quadriplegia after the insertion of an intrathecal baclofen pump. Spine. 2007;32:2745-2750
Study Type / Methods	Pre- and post-intervention study conducted at the University of Nebraska Medical Centre. The aim of the study was to quantify scoliosis progression in spastic quadriplegic patients before and after baclofen administration and compared this to published natural history data. To document the magnitude and rate of scoliosis progressions after the placement of an ITB pump, the charts and radiographs of 19 consecutive non ambulatory patients with spastic quadriplegia and an ITB pump were reviewed. To document the rate of scoliosis progression, each patient had at least 2 pre and 2 post pump insertion spinal radiographs made. A board certified orthopaedic surgeon reviewed these radiographs. Skeletal maturity was assessed using Risser grading. Catheter tip location and rate of baclofen administration were recorded. The rates of scoliosis were then compared with the natural history studies of scoliosis progression in similar populations.
LE	II-2
Number of Patients and Patient Characteristics	19 non ambulatory patients with spastic quadriplegia: • 12 males • 7 females • Patients ages ranged from 1 year 11 months to 19 years at the time of pump insertion • 6 patients were skeletally mature (Risser 5) at the time of pump insertion • 13 patients were skeletally immature at the time of pump placement • All patients had long C-shaped thoracolumbar curves
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Average 20.9 months after ITB insertion and 23.9 months after surgery
Outcome measures/ Effect size	**Progression of scoliosis (Cobb angles)** Pre and Post ITB Cobb angles: • Average Cobb angles were 10.2° before pump insertion and 25° at an average of 20.9 months after pump insertion (P< 0.0001) • Mean rate of change in their Cobb angles of 1.825%/year before pump insertion and 10.95%/year at an average of 23.9 months after pump insertion (P = 0.024). These results represent a 6-fold increase in the curve progression rate after pump insertion. • There was no association between catheter tip location or rate of Baclofen infusion on curve progression **Authors conclusion** In published data, the rate of progression of scoliosis in skeletally immature non ambulatory patients with cerebral palsy was 4.5°/year. In this study average rate of progression of the scoliosis for the immature was 9.02°/year. For the skeletally mature bed-ridden patients, the worst-case natural history progression was 4.4°/year. The comparable rate of change in skeletally mature (Risser 5) nonambulatory patients in this study was 28.4°/year. This study demonstrates a significant increase in the rate of scoliotic curve progression after ITB pump placement when compared with published natural history data.
General comments	Retrospective

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Bibliographic Citation	37. Senaran H, Shah SA, Presedo A, Dabney KW, Glutting JW, Miller F. The risk of progression of scoliosis in cerebral palsy patients after intrathecal baclofen therapy. Spine. 2007;32:2348-2354
Study Type / Methods	Pre- and post-intervention study with matched control group conducted at a single institution in Turkey. The aim of the study was to identify the effect of intrathecal baclofen on the incidence of scoliosis, rate of curve progression, and pelvic obliquity compared with a matched cohort. All patients with spastic CP treated with ITB between 1997 and 2003 at a single institution were reviewed. A total of 107 patients undergoing ITB for a minimum of 2 years were identified, of which 26 patients subsequently developed or had a progression of scoliosis. Twenty five age, gender, and gross motor function classification system (GMFCS) score-matched quadriplegic CP patients with scoliosis who did not receive ITB were selected from a database and constituted the control group used to compare the rate of curve progression and pelvic obliquity. In the baclofen group, patients who had <15 º of scoliosis demonstrated by radiographs at the time of pump implantation were identified and the incidence of ITB at minimum 2 year follow-up was calculated. In order to define the incidence of scoliosis in the quadriplegic CP population without ITB, a preliminary study was conducted and the patients who reached 18 years of age between 1997 and 2003 were screened.
LE	II-2
Number of Patients and Patient Characteristics	Baclofen group: 26 patients • All had spastic quadriplegic CP • 14 males, 12 females • Mean age at pump implantation was 11.8 years (range, 5 to 18 years) • Mean age at follow up was 14.8 ± 3.4 years (range, 9 to 21 years) • 2 patients were classified as GMFCS 4, 24 as GMFCS 5 Control group: 25 patients • Had quadriplegic CP • 15 males, 10 females • Mean age at diagnosis of scoliosis was 11.6 ± 3.5 years (range, 5 to 18 years) • 3 patients were GMFCS 4 and 22 were GMFCS 5
Intervention	Continuous ITB infusion , Programmable pump (Synchromed EL or II, Medtronic Inc., Minneapolis, MN)
Comparison	Not treated with ITB
Length of follow up (if applicable)	Baclofen group; mean follow-up was 2.9 years (range, 2 to 7 years) Control group; mean follow-up was 4.0 years
Outcome measures/ Effect size	**Progression of scoliosis** Baclofen group versus control group: • Average curve progression for the baclofen group after pump implantation was 16.3º per year, and for the control group was 16.1º per year. • Both groups curves progressed over time during growth (P = 0.001, but baclofen did not have an independent effect on curve progression (P = 0.181) • Average pelvic obliquity for the 2 groups increased over time (P = 0.001), but there was no difference between the groups (P = 0.536) **Incidence of scoliosis** Baclofen group versus control group: • In the Baclofen group, 57 patients had no scoliosis or curve < 15° at pump implantation. Twelve of 57 patients (21%) developed scoliosis after pump implantation during a mean of 3.6 years of follow-up • 30 of 92 matched control patients (32%) not treated with ITB within the same interval had scoliosis by maturity **Authors conclusion** This study demonstrate that ITB has no significant effect on curve progression, pelvic obliquity, or the incidence of scoliosis when compared with an age, GMFCS score matched control group of patients with spastic CP without ITB.
General comments	Retrospective

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Bibliographic Citation	38. Shilt JS, Lai LP, Cabrera MN, Frino J, Smith BP. The impact of intrathecal baclofen on the natural history of scoliosis in cerebral palsy. J Pediat Orthop. 2008;28:684-687
Study Type / Methods	Pre- and post-intervention study (with matched control group conducted at the Wake Forest University School of Medicine. The aim of the study was to further examine the effect of ITB treatment on the progression of scoliosis in patients with cerebral palsy. Paediatric patients who received ITB treatment between 2000 and 2005 were recruited and followed in the multidisciplinary paediatric spasticity clinic of the Department of Orthopaedic Surgery at the Wake Forest University School of Medicine. Baseline Cobb angles of the primary curve were measured during the period of ITB pump insertion and at the most recent follow-up. For each ITB patient, a control patient was matched by age, sex, topographical involvement, and an initial Cobb angle within 10 degrees. Control patients were identified from the multidisciplinary spastic database, which includes all patients with spasticity at the Wake Forest University School of Medicine. The mean rate of change in the Cobb angle was compared between ITB and control patients using paired t test. A multiple linear regression model was used to examine the difference, controlling for age, sex, topographic involvement, and initial Cobb angle.
LE	II-2
Number of Patients and Patient Characteristics	ITB patients (n= 50): • Quadriplegic 86% • 38% females • Mean age(SD), range=9.8 (3.7), 3.6-16.7 • Initial Cobb angle, mean (SD), range =15º(13º),0-76º Control patients (n=50): • Quadriplegic 86% • 38% females • Mean age(SD), range=9.7 (3.9), 3.4-16.9 • Initial Cobb angle, mean (SD), range =13º(13º),0-67º
Intervention	Continuous ITB infusion
Comparison	Not treated with ITB
Length of follow up (if applicable)	ITB patients; mean follow-up was 2.7 (SD, 1.4 years) range, 0.2 to 6.3 years) Control group; mean follow-up was 3.0 (SD, 1.6 years) range, 0.3 to 6.9 years)
Outcome measures/ Effect size	**Progression of scoliosis** ITB patients versus control patients (Mean annual progression of Cobb angle): • There was no statistically significant difference between the mean change in Cobb angle in ITB patients (6.6 degrees per year) compared with the matched control patients (5.0 degrees per year), P = 0.39. • Multiple linear progression showed that adjusting for age, sex, topographic involvement, and initial Cobb angle, the mean progression of Cobb angle was 0.92 degrees per year greater in ITB group compared with controls, P = 0.56 **Authors conclusion** The progression of scoliosis in cerebral palsy patients with ITB treatment is not significantly different from those without ITB treatment. The findings suggest that patients receiving ITB experience a natural progression of scoliosis similar to the natural history reported in the literature.
General comments	

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Bibliographic Citation	39. Jones ML, Leslie DP, Bilsky G, Bowman B. Effect of intrathecal baclofen on perceived sexual functioning in men with spinal cord injury. J Spinal Cord Med. 2008;31:97-102
Study Type / Methods	Pre- and post-intervention study conducted at Atlanta Georgia. The aim of the study was to examine, prospectively and with a standardised measure of sexual function, the impact of intrathecal baclofen on perceived sexual functioning in men with severe spasticity of spinal origin. Seven adult men with spinal cord injury [SCI (ASIA A or B)] who received intrathecal baclofen through an implantable pump for treatment of severe spasticity were followed for an average of 670 days (22.4 months) after implant. Perceived sexual function was assessed using Brief Sexual Function Inventory (BSFI). BSFI consists of 11 items covering 5 aspects of sexual functioning: sexual drive (2 items), erection (3 items), ejaculation (2 items), perception of problems with sexual function in each areas (3 items), and an overall satisfaction rating (1 item). Participants were asked to complete questionnaires before pump implantation and monthly for 3 months and then approximately 4 months for up to 2 years after implant. Severity of spasticity and overall health-related quality of life were assessed.
LE	II-2
Number of Patients and Patient Characteristics	7 participants with severe spasticity secondary to traumatic spinal cord injury: • Mean age, 36.7 years • Mean months post injury, 41.9 months Inclusion criteria: • Men 25 to 45 years of age • SCI • Positive bulbocavernous reflex, indicating capacity for reflexogenic reactions • Reported history of sexual activity since injury
Intervention	Continuous ITB infusion
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up interval = 670 days
Outcome measures/ Effect size	Perceived sexual functioning before and after ITB treatment: • Participants indicated generally unchanged or improved ratings of perceived sexual functioning after implant • 2 of 7 participants reported some negative changes in sexual function after baclofen pump implant, noted in the areas of reduced sex drive and problems with erections (frequency, rigidity, difficulty in achieving) • 2 participants reported marked improvement in perceived sexual function from pre to post implant • Analysis of changes in perceived sexual function over time suggest that problems may be associated with an increase in baclofen dose and may be reversible with a reduction in dose **Authors conclusion** Intrathecal baclofen may impact perceived sexual function particularly at higher doses. However, the effects seem to be reversible with withdrawal or reduction of baclofen administration.
General comments	Retrospective

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with for spasticity?

Bibliographic Citation	40. Denys P, Mane M, AzouviP, Chartier-Kastler E, Thiebaut JB, Bussel B. Side effects of chronic intrathecal baclofen on erection and ejaculation in patients with spinal cord lesions. Arch Phys Med Rehabil.1988;79:494-496
Study Type / Methods	Pre- and post-intervention study conducted in France. The aim of the study was to assess modifications of sexual function in men treated with intrathecal baclofen for spinal spasticity. A convenient sample of nine consecutively recruited men with spinal cord injury (SCI) or multiple sclerosis who were receiving intrathecal baclofen by an implantable pump were assessed clinically with a questionnaire given to the patient during personnel interview before pump implantation and after pump implantation. The questionnaire focused on the following aspects: the ability to sustain reflexive and psychogenic (without any local stimulation) erections and to obtain ejaculation without any electrical, vibratory or pharmacologic stimulation, assessed by a yes / no score; penile rigidity during erection, evaluation by a visual analogue scale on which 100% meant maximal rigidity and 0% no erection at all. Patients were also questioned about possible modification of libido before and after implantation.
LE	II-2
Number of Patients and Patient Characteristics	9 participants with severe spasticity secondary to spinal cord injury or multiple sclerosis: • Age range from 29 years to 51 years • 5 had SCI, 4 had multiple sclerosis
Intervention	Continuous ITB infusion, Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	Average follow-up was 44.4 months
Outcome measures/ Effect size	Genitosexual Function Before and After ITB treatment: • Libido and ability psychogenic or reflexogenic erections were not modified • However, 8 patients reported a decrease of erection rigidity and / or duration • Ejaculation was possible in 3 cases before implantation, it disappeared in 2 patients, and more difficult to obtain in the last one. In the 2 patients ejaculation reappeared during temporary unexpected treatment withdrawal (because of catheter or pump dysfunction) • No differences was found between multiple sclerosis and spinal cord injured patients **Authors conclusion** Intrathecal baclofen may seriously compromise erection and ejaculation. In most cases, the beneficial effect on spasticity outweighed the deleterious effect on sexual function. None of the patients asked for treatment interruption. It should be stressed that the inhibitory effect is reversible. Nevertheless, patients should be informed on this possible effect (as well of its reversibility), which should be considered before any decision on pump implantation.
General comments	

Evidence Table : COST- EFFECTIVENESS
Question : Is Continuous ITB infusion cost-effective for treatment of patients with spasticity?

Bibliographic Citation	1. Hoving MA, Evers SMAA, Ement AJHA, van Raak EPM, Vles JSH. Intrathecal baclofen therapy in children with spastic cerebral palsy: a cost-effectiveness analysis. Development Medicine & Child Neurology. 2008;50:450-455
Study Type / Methods	Cost-effectiveness analysis (CEA) / cost-utility analysis (CUA) analysis conducted at University Hospital Maastricht, Netherlands. Aim of this combined CEA / CUA was to evaluate the cost-effectiveness of CITB in the treatment of children with intractable spastic cerebral palsy (CP). **Method** This combined CEA / CUA was embedded in the Dutch national study on the efficacy and safety of CITB for intractable spasticity in children with CP. Study design, time horizon and perspective: Compared the costs and health effects of continuous intrathecal baclofen infusion (CITB) and standard treatment only, for a 1 year period. Patients received only standard treatment in the year preceding the test treatment versus CITB in addition standard treatment from the pump implantation onwards. Standard treatment included physical therapy, and / or rehabilitation. For the assessment of the additional costs of CITB, the costs in the year before the test treatment were compared with the costs in the first year after the pump implantation (before-after comparison). For the assessment of the additional health effects of CITB, the visual analogue scale (VAS) was used for individual problems in the CEA and the EuroQoL-5D (EQ-5D) in the CUA. They compared the values at the 1-year follow-up visit with those obtained before pump implantation (baseline). The perspective of both the CEA and CUA was that of the health care. Data collection, data sources and costs: Included intervention costs and other health care costs. For health care costs, data were collected by means of a questionnaire and a cost diary. The questionnaire included the following health care resources: general practitioner care, outpatient specialist medical care, alternative therapies, emergency department attendances, ambulance transfers, hospitalisations, tests and prescribed medication. Intervention costs included expenditure for the test treatment phase, the pump implantation phase, and the pump refills. Majority of the costs were valued using the Dutch guidelines for pharmacoeconomic research and real unit prices excluding taxes, as assigned by the University Hospital Maastricht. Costs were estimated for the year 2003 in Euros. Discounted costs that were not available for the year 2003 with 4% per year according to Dutch guidelines. Outcome measures: Formulated three problems per patient and used the average of these three VAS scores for statistical analyses. The EQ-5D has been developed to generate a single index for health status for use in economic evaluations. Cost-effectiveness: Participants with both cost and effectiveness data were included in the CEA and CUA. Bootstrap method was used to verify the reliability of the results.
LE	
Number of Patients and Patient Characteristics	15 patients: • 8 females, 7 males • Age between 7 and 17 years (mean age 13 years 8 months, SD; 3 years) • 11 children had spastic CP, 4 had spastic –dyskinetic CP Gross Motor Function Classification System: 1 level III, 2 level IV, 11 level V
Intervention	Intrathecal infusion of baclofen and standard treatment. Programmable infusion pump (Medtronic Inc., Minneapolis, Minnesota)
Comparison	Standard treatment only
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**CEA / CUA** Costs: • Total mean annual costs for standard treatment only = £5,296 • Total mean annual costs for CITB and standard treatment only = £9,028 • Additional mean annual costs of CITB = £3,732 Costs-effectiveness: • VAS for individual problems improved from 2.3 (SD, 1.1) at baseline to 7.2 (SD, 1.7) after 1 year of CITB (P = 0.001) • On the cost-effectiveness plane, all point estimates were found in the same quadrant. This means that CITB was more effective and more costly than standard treatment only. Cost-utility: • On the cost-utility plane derived from the Dutch EQ-5D index, all point estimates were found in the same quadrant. This means that CITB was more effective and more costly than standard treatment only. • The cost utility plane derived from the UK EQ-5D index showed no appreciable difference • One QALY cost an average £32,737, using the Dutch EQ-5D index, and £28,273, using UK-5D index. **Authors conclusion** Our results confirm the cost-effectiveness of CITB for carefully selected children with intractable spastic CP and, from an economic point of view, justify the reimbursement of CITB for this group of patients in the Netherlands (threshold willingness to pay for one QALY in the Netherlands, £80,000).
General comments	

Evidence Table : COST- EFFECTIVENESS
Question : Is Continuous ITB infusion cost-effective for treatment of patients with spasticity?

Bibliographic Citation	2. de Lissovoy G, Matza LS, Green H, Werner M, Edgar T. Cost-effectiveness of intrathecal baclofen therapy for treatment of severe spasticity associated with cerebral palsy. J Child Neurol. 2007;22(1):49-59
Study Type / Methods	Cost-utility analysis (CUA) conducted in the USA. Aim of this analysis was to assess the cost-effectiveness of intrathecal baclofen among children with severe spasticity of cerebral origin who have not responded to less invasive treatments such as oral medications relative to alternative medical and surgical therapy. **Method** Used mathematical modelling and computer simulation to estimate the incremental cost per quality-adjusted life-year for identical cohorts of 20 children treated with intrathecal baclofen or alternative therapy over 5-year episode of treatment. Data on treatment costs representative of these children were derived from a health insurance claims database that included both commercial and Medicaid data. Utility values used to construct quality- adjusted life years were obtained from a panel of 9 expert clinicians who used the Health Utilities Index-2 to rate health states associated with course of treatment.
LE	
Number of Patients and Patient Characteristics	Mean / median age of study population was younger than 18 years:
Intervention	Intrathecal baclofen therapy
Comparison	Conventional medical therapy
Length of follow up (if applicable)	5 years
Outcome measures/ Effect size	**CUA** Base case: • Mean Incremental Cost with Intrathecal Baclofen Therapy = USD $ 49,400 • Incremental Quality-Adjusted Life years with intrathecal baclofen therapy = 1.19 • Incremental Cost per Quality-Adjusted Life years with intrathecal baclofen therapy = USD $ 42,000 (interquartile range, USD $ 36,700 to USD $ 62,200) Sensitivity analysis: • Scenario 1 (quality adjusted life year patients had a 25% annual risk of adverse events during years 3 to 5) ◦ Incremental Cost per Quality-Adjusted Life years with intrathecal baclofen treatment complications = USD $ 45, 700 (interquartile range, USD $ 34,000 to USD $ 56,500) • Scenario 2 (annual cost for alternative therapy increased at an annual rate of 10%) ◦ Incremental Cost per Quality-Adjusted Life years with increasing complexity of alternative care = USD $ 31, 500 (interquartile range, USD $ 20,800 to USD $ 42,300) **Authors conclusion** Our results indicate that intrathecal baclofen delivered via an implantable pump in appropriately selected paediatric patients offers a good value for the money based on widely accepted measures of cost-effectiveness.
General comments	

Evidence Table : COST- EFFECTIVENESS
Question : Is Continuous ITB infusion cost-effective for treatment of patients with spasticity?

Bibliographic Citation	3. Bensmail D, Ward AB, Wissel J, Motta, Saltuari L, Lissens J, Cros S, Beresniak A. Cost-effectiveness modelling of intrathecal baclofen therapy versus other interventions for disabling spasticity. Neurorehabilitation and Neural repair. 2009; 23(6):546-552
Study Type / Methods	Cost-effectiveness analysis conducted in France. Aim of this analysis was to assess by simulation the cost-effectiveness of intrathecal baclofen (ITB) therapy compared with conventional medical treatment for patients with disabling spasticity and functional dependence caused by any neurological disease. **Method** Two simulation models were created to simulate therapeutic strategies for managing severe spasticity, one with and one without the use of ITB, to assess various treatment sequences over 2 years based on current medical practices in France. Successful treatment at each evaluation was defined as a combination of: (1) the increased patient and caregiver satisfaction as assessed by goal attainment scaling (GAS), and (2) a decreased of at least 1 point on the Ashworth score. Probabilities sensitivity analysis were performed using 5000 Monte-Carlo simulations taking into account specific distribution curves for direct costs and effectiveness parameters in each treatment option.
LE	
Number of Patients and Patient Characteristics	
Intervention	Intrathecal baclofen therapy
Comparison	Conventional medical treatment
Length of follow up (if applicable)	2 year
Outcome measures/ Effect size	• The model simulation established that using ITB as a first strategy in severely impaired patients with disabling spasticity had a significantly higher success rate than conventional medical management (78.7% versus 59.3%, P < 0.001) • Despite the fact that ITB acquisition costs were the highest among antispastic treatments, the ITB treatment regimen (when used as a first option strategy) resulted in a significantly lower total medical cost (£59,391 versus £88,272; P < 0 ,001) over the 2 year model time horizon • ITB was considered to be the dominant strategy providing greater effectiveness at a lower cost • The mean cost-effectiveness ratios show a significantly lower average cost per success with ITB as a first-line strategy (£75,204 / success versus £148,822 / success, P < 0.001) **Authors conclusion** Within the assumptions of our modelling, ITB therapy evaluated by a combination of treatment success criteria at 6-months interval over a 2-year period maybe a cost-effective strategy compared with conventional medical management alone.
General comments	

Evidence Table : COST- EFFECTIVENESS
Question : Is Continuous ITB infusion cost-effective for treatment of patients with spasticity?

Bibliographic Citation	4. Hattori N, Hirayama T, Katayama Y. Cost-effectiveness analysis of intrathecal baclofen therapy in Japan. Neurol Med Chir. 2012;52:282-287
Study Type / Methods	Cost-utility analysis (CUA) conducted at Nihon University School of Medicine, Tokyo. Aim of this analysis was to assess ITB therapeutic efficacy for lucid patients with severe spasticity receiving home care with regard to cost-utility and quality of life (QOL) improvement. **Method** Six subjects underwent a primary survey 1 year after surgery. The degree of spasticity was evaluated before and 1 year after surgery using Ashworth score. Activities of daily living (ADL) were evaluated using modified Rankin scale. Quality of life (QOL) was evaluated before and 1 year after surgery according to EQ-5D Japanese version using information obtained from the patients themselves. The medical costs were divided into direct cost (DC) and indirect cost (IC). The DC was based on the charges made by the hospitals and clinics for each patient and adjusted to the cost in April 2009. The IC was calculated on the basis of the estimated production loss of the patient and their family members who were responsible for nursing at home, using the Wages Census, a fundamental statistic of wages and salary structure (2009). Utility scores before and after surgery was multiplied by the number of years of activity to calculate the quality-adjusted life years (QALY) for each patient. Sensitivity analyses were performed to consider the effect of changes in costs (discount rate 0-10%).
LE	
Number of Patients and Patient Characteristics	6 severely spastic patients admitted to university hospital between 2005 to 2010 for ITB therapy: • 5 men • 1 woman • Mean age of 41.5 years Diagnosis: 2 spinal cord tumours, 2 head injury, 1 cerebral stroke, 1 spinal injury, 1 spinal tumour
Intervention	Intrathecal baclofen therapy
Comparison	Conventional medical therapy
Length of follow up (if applicable)	5 years
Outcome measures/ Effect size	**CUA** Effects of ITB therapy (mean): • Mean Modified Rankin scale was 3.83 before ITB decreased to 2.33 after ITB therapy • Mean Ashworth score was 3.17 before ITB decreased to 2.04 after ITB therapy • QOL value (utility) was 0.242 increased to 0.662 after ITB therapy Effects on medical costs: • Direct medical cost/month was 37,500 Japanese yen before ITB increased to 46,000 Japanese yen after ITB therapy • Indirect medical cost/month was 613,170 Japanese yen before ITB decreased to 511,443 Japanese yen after ITB therapy **Cost-effectiveness:** • Base case: ◦ Average cost of ITB therapy per QALY 5 years after surgery was 1,554,428 Japanese yen **Sensitivity analysis:** • Best case: ◦ Average cost of ITB therapy per QALY 5 years after surgery was 1,533,035 Japanese yen • Worst case: ◦ Average cost of ITB therapy per QALY 5 years after surgery was 1,582,528 Japanese yen **Authors conclusion** The average cost of ITB therapy per QALY was below the 6 million yen willingness-to-pay threshold for 1 QALY. This study shows that ITB therapy in Japan is an outstanding treatment in medicoeconomic terms.
General comments	

DYSTONIA
Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	1. Motta F, Stignani C, Antonello CE. Effect of intrathecal baclofen on dystonia in children with cerebral palsy and the use of functional scales. J Pediatr Orthop. 2008;28(2):213-217
Study Type / Methods	Pre- and post-intervention study. Study was conducted at the Department of Paediatric Orthopaedics at BV. Buzzi Children's Hospital, in Milan. between January 2000 and October 2005 The aim of this study was to evaluate, with the use of functional scales, the effect of ITB on generalised dystonia in 19 patients affected by CP and with severe degree of impairment. Standard video recordings were used to assess dystonia with 2 different rating scales: • The Barry-Albright Scale (BAD)-evaluates secondary dystonia in 8 regions of the body (eyes, mouth, neck, trunk, upper limbs, and lower limbs) and gives each a score from 0 to 4 • The Burke-Fahn-Marsden rating scale (BFM) - to evaluate primary dystonia but can also be used for secondary dystonia and consists of 2 sections: the movement scale, based on patient observation, and the disability scale, based on the patient's everyday activity. Inclusion criteria: • Dystonic CP • Belonging to level V of Gross Motor Function Classification System (GMFCS) • Age at implant below 18 years The patients were reassessed using the same rating scales at 3, 6, and 12 months postimplant. The surgical implant technique was modified in March 2003. Initially, the pump was positioned subcutaneously, whereas the modified technique positions the pump more deeply into the abdomen, under the external oblique muscle, and the abdominal rectus: • 14 patients subfascial technique • 5 patients subcutaneous implant technique • The catheter was positioned at level C1 for all 19 patients. Of all 19 patient: ◦ 9 were implanted with SynchroMed EI pump with a reservoir size of 10 mL, ◦ 1 patient, used a SynchroMed EI with a reservoir size of 18 mL. ◦ 10 patients were implanted with a SynchroMed II pump with a reservoir size of 20 mL. All patients were given a subjective internal questionnaire at each follow-up: 26 questions - various aspects of the patient's life (daily activity, movement, autonomy, pain, sleeping, performance at school, communication, use and tolerance of aids, and mood) given to the patient or to the caregiver if the patient was unable to communicate.
LE	II-2
Number of Patients and Patient Characteristics	19 patients: • 13 males and 6 females, with an age at implant of between 2 years 5 months and 16 years and 6 months • Mean age was 8.49 years, (SD = 3.2 years) • All of whom had dystonia associated with CP • All 19 patients, 13 (70%) were affected by spastic / dystonic tetraplegia with severe generalised dystonia • 6 (30%) patients were affected by dystonic tetraplegia
Intervention	Intrathecal baclofen infusion 18 patients - continuous infusion, 1 patient - daily periodic bolus infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Efficacy of continuous intrathecal infusion of baclofen (differences between preimplant and after ITB treatment) • Statistically significant improvement between the follow-up and preimplant scores in both evaluation scales ($P < 0.001$), after 3 months and maintained for the 12 months of follow-up. Barry-Albright Scale (BAD) total score: • Decreased in the average BAD score [baseline = 23.84 (SD, ± 4.11), at 12 months postimplant 17.79 (SD, ± 3.3] • 25% improvement of average BAD total score at 12 months postimplant compared with baseline in all patients Burke-Fahn-Marsden rating scale (BFM) total score: • Statistically significant in overall improvement ($P < 0.001$) in BFM • Decreased in the total BFM score [baseline 98.57 (SD ± 13.07), at 12 months 77.60 (SD ± 20.56)] • None of the patients showed any change regarding everyday activities because all patients studied belonged to GMFCS level V and so were affected by severe limitations in terms of autonomy and the need for assistance in everyday activities Correlation between BAD and BFM scale: Positive correlation between the BAD and BFM scale (0.59, P = 0.05) Subjective questionnaires result • Eighteen patients (95%) showed an improvement in the dystonias, whereas 1 (5%) exhibited no change • The caregivers reported an improvement in patient management, (hygiene, dressing, feeding, and daily movement) • Improvement in posture control and upper limb • Around half of the patients showed animprovement in sleeping (10 of 19 patients) and in mood (9 of 19 patients),68% of caregivers reported no change in the area of autonomy • 15 patients (9%) stated that they were satisfied with the implant and most (14 of 19 patients) would do it again, 3 (16%) were not totally satisfied and were uncertain as to whether they would do it again, 1 (5%) expressed dissatisfaction and would not undergo implant again and he chose to explant pump 4 years after implant, two (11%) of the 19 patients had the device removed: dissatisfaction 4 years after the implant and infection occurred 14 months after implant. **Authors conclusion** In patients belonging to level V of Gross Motor Function Classification System and treated with ITB, a decrease in frequency and severity of dystonia is observed. The improvement eases caregiver in patient management.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	2. Motta F, Antonello CE, Stignani C. Upper limbs function after intrathecal baclofen therapy in children with secondary dystonia. J Pediatr Orthop. 2009; 29(7):817-821.
Study Type / Methods	Pre- and post-intervention study. Study was conducted at paediatric department at "V Buzzi" Children Hospital, Milan between January 2006 and September 2007. The aim of this study was to determine the effects of ITB therapy in patient with secondary dystonia due to cerebral palsy, in addition to reducing dystonia and also improve upper limb function **Inclusion criteria** Patients whose dystonia was sufficiently severe to cause problems in performing everyday life activities, who were able to sit without support or with their seating system and to perform the tasks required by Melbourne assessment of unilateral upper limb function scale (MUUL) without wrist and elbow contractures, and who had not had botulin toxin A injection in the upper limbs in the previous 6 months before implant. Evaluation baseline and post implant: • Upper limb function assessment was conducted using MUUL • Dystonia assessment using BAD. • The preimplant assessment and the follow-ups were conducted by the same team consisting of 2 physiotherapists In all the 11 patients, the pump were positioned using the subfascial technique, the catheter was positioned at level C1
LE	II-2
Number of Patients and Patient Characteristics	11 patient with secondary dystonia, classified as level III and IV of the Gross Motor Function Classification System: • 4 males and 7 females • 7 patients – level III, 4 patients- level IV • Mean age at implant 11.3 years (SD ± 3.02) years
Intervention	Continuous intrathecal baclofen.
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Efficacy of continuous intrathecal infusion of baclofen (differences between preimplant and after ITB treatment) Melbourne assessment of unilateral upper limb function scale (MUUL) total percentage score: • Significant improvement in both the dominant and the non dominant limb ($P < 0.05$) • Dominant limb - increased in MUUL total average percentage score from [baseline 46.42% (SD ± 19.6 %), at 12 months 55.44% (SD ± 17.4 %) • Non dominant limb - total score improved in 10 of 11 patients and worsened in 1 case: [baseline 32.19% (SD ± 18.9 %), to 40.61% (SD ±15 %) at 12 months] • Score variation ≥12% in 4 patients (36%) for the dominant limb and 4 patients (36%) for the non dominant limb. This value was considered clinically significant Barry-Albright Scale (BAD) total score: • Dystonia decreased significantly by 15% from baseline to 12 months follow up ($P < 0.05$). At baseline, average percentage of BAD total score was 63.35 (SD ±19.9 reduced to 48.01 (SD ±14.9) at 12 months post implant • 8/11 (73%) patients had decreased in BAD score related to upper limbs [baseline 6.7 (SD ± 1.2), at 12 months 5 (SD ± 1.3) ($P < 0.05$)] Interview: All caregivers reported improvements in patient management (i.e. hygiene, dressing, and daily movement) and improved posture and use of the upper limbs. Infusion dosage: Mean dose recorded at follow-up was 311 (SD =133). **Authors conclusion** In patients with secondary dystonia treated with ITB, functional improvement of the upper limb limbs was observed in addition to dystonia reduction. In patients with secondary dystonia, ITB is the treatment that aims to achieve a general reduction of dystonia; this study want to show the influence that this reduction has to functional ability of patient.
General comments	

Evidence Table : EFFECTIVENESS

Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	3. Albright AL, Barry MJ, Shafton DH, Ferson SS. Intrathecal baclofen for generalized dystonia. Developmental Medicine & Child Neurology. 2001;43:652-657.
Study Type / Methods	Pre- and post- intervention study. This study was conducted in Children Hospital of Pittsburgh, USA. The aim of the study was to evaluate the effects of intrathecal baclofen (ITB) on patients with severe generalised dystonia. Participants were evaluated between October 1993 and August 1999. Participants had dystonia that interfered with function, or comfort and had BAD scores of 3 to 4 in at least major body regions (extremities, trunk, neck). Most participants were severely developmentally and motorically delayed; Gross Motor Function Classification System levels were II in 2%, III in 2%, IV in 11%, and V in 85% of participants. Before insertion of a pump, responsiveness to ITB was usually tested. After pump implantation, participants were re-evaluated in clinic at 3, 6, 12, and 24 months using Barry-Albright Dystonia (BAD) score, then yearly for 5 years. BAD scores pretreatment were compared with scores at those time intervals using repeated measures of analysis variance (ANOVA). The present report includes patients with at least 1 year follow-up. Parents, caregivers, or participants were contacted by telephone and questioned about the effects of ITB as of September 2000.
LE	II-2
Number of Patients and Patient Characteristics	86 participants • All had generalised dystonia • Age ranged from 3 to 42 years, with a mean age of 14 years and a median of 13 years • Of the 86 participants with dystonia, 33 had coexisting spasticity, but their dystonia was the predominant movement disorder
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	5 years, median 29 months
Outcome measures/ Effect size	**Screening phase:** Performed in 83 participants: 69 by continuous infection and 14 by bolus injection Of 69 participants with continuous infusion: • 63 responded with clinically significant decreased in their mean dystonia scores • 3 had equivocal responses • 3 had no response • Mean infusion dose was 485µg/day Of 14 participants with bolus injection: • 13 of 14 participants responded to the bolus injections Pumps were inserted in 77 participants. 1 year follow-up data were not available in 7 participants whose pumps were removed because of infection or persistent CSF leak. ITB therapy: • Mean and median BAD scores before pump implantation were 18 • Mean BAD score (baseline = 18, 3 months = 13, P = 0.003; 6 months = 10, P = 0.001, 12 months = 7, and 24 months = 10, $P \leq 0.001$) • Mean dystonia scores were significantly lower in participants whose intrathecal catheters were positioned at T4 or higher compared to those at T6 or lower (BAD Score 4 versus 10, P = 0.005) • 92% of participants retained response to ITB during a median follow-up 24 months • 8% lost their response during chronic treatment, usually during the first year after implantation Telephone survey on effect of ITB: • 85% reported that the pump was "worth it" • Improved quality of life (85%) • Ease of care (86%) • Improved speech (33%) • Improved swallowing (26%) • Improved upper extremity function (34%) • Improved lower extremity function (37%) **Authors conclusion** ITB appears to be the treatment of choice for severe generalised dystonia, particularly secondary dystonia which is inadequately treated by oral medications. Ease of care improves in 86% and function improves in one third of patients. Although approximately 8% of patients lose their responsiveness to ITB, it has been effective in the remainder for up to 7 years.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	4. Walker RH, Danisi FO, Swope DM, Goodman RR, Germano IM, Brin MF. Intrathecal baclofen for dystonia: benefits and complications during six years of experience. Movement Disorders. 2000;15(6):1242-1247.
Study Type / Methods	Pre-and post-intervention study. The study was conducted at Mount Sinai Medical Centre. Pumps were implanted between June 1993 and May 1998. Reviewed the charts of all patients. Fourteen patients with primary or secondary dystonia received intrathecal baclofen (ITB) through an implanted pump following a trial dose. Patients were selected for ITB trial if they had clinically unsatisfactory response to oral antidystonic medications, including oral baclofen. After pump implantation, the dose of ITB was increased in increments of approximately 10% until either the patient reported dose-limiting adverse effects or a dose of 1000 µg /day. Patients were rated using the Burke-Fahn Marsden (BFM) rating scale scores by a blinded rater after the dose of ITB were optimised.
LE	II-2
Number of Patients and Patient Characteristics	14 patients with dystonia: 8 had primary generalized dystonia,1 primary cranial segmental dystonia, 5 had secondary dystonia
Intervention	Intrathecal infusion of baclofen After pump implantation, the dose of ITB was increased in increments of approximately 10% until either the patient reported dose-limiting adverse effects or a dose of 1000 µg /day
Comparison	No comparator
Length of follow up (if applicable)	Mean length therapy -29 months (range 6-64 months)
Outcome measures/ Effect size	• Trial Dose: ◦ All patients reported positive response except one patient ◦ Mean dose = 590 µg/day (50-1000 µg/day) • Post pump implantation: ◦ Of 14 patients with dystonia, 5 patients experienced improvement in symptoms (objective benefit) as determined by a change in rating scale scores, although only 2 had a clear clinical benefit • Primary dystonia: ◦ 7 of 9 patients with primary dystonia had videotaped evidence to perform BFM ratings on and off ITB. Of these, decreased in BFM scores were seen in 3 patients. • Secondary dystonia: ◦ 5 patients with secondary dystonia had videotaped evidence to perform BFM ratings on and off ITB. Of these, 2 demonstrated objective clinical benefit **Authors conclusion** Aetiology of dystonia did not determine the efficacy of ITB therapy, as benefit or failure was seen in both primary and secondary dystonia.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	5. Woon K, Tsegaye M, Vloeberghs MH. The role of intrathecal baclofen in the management of primary and secondary dystonia in children. Br J Neurosurg. 2007.21(4):355-358.
Study Type / Methods	Cross sectional study. The aim of this study was to review the safety and efficacy of ITB in children with dystonia. Study was conducted at the University Hospital Nottingham. From October1998 to May 2006, there were 112 ITB pump implantations in 104 children with spasticity of cerebral origin. Reported the result of prospectively collected audit database. From the database, information was obtained on patients who had intrathecal baclofen pump insertion for spasticity or dystonia. The indications for ITB in dystonia were painful muscle spasms, severe spasticity, and to improve deteriorating nursing care. Subsequent assessment regarding improvement in general handling and posture were undertaken by the patient's carers. Further assessments on the effectiveness of the test procedure were also made by the physiotherapists and nurses.
LE	II-3
Number of Patients and Patient Characteristics	104 children with spasticity of cerebral origin (67 males and 37 Female). Age range from 4 to 20 years Eight children (four females, four males) had ITB pump implantation for spasticity and dystonia: • Mean age of 12.5 years, range 10 to 18 years. • 1 had glutaric aciduria type 1 • 1 had Leigh' syndrome, • 1 had idiopathic dystonia • 3 had panthotenate kinase associated neuronal degeneration (PKAN) • 2 had dystonia secondary to cerebral palsy • 2 had previous treatment with deep brain stimulation (DBS) • 1 who had ITB inserted, subsequently have DBS inserted
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	
Outcome measures/ Effect size	• In all 8 children, carers reported a marked improvement in nursing care • In addition to reduction in spasticity and ease of nursing care, other benefits were noted: improved in sitting and sleeping, better control of head and arms, and less writhing movement • Improvement was most marked in children who had dystonia secondary to cerebral palsy • Synergistic improvement of both spasticity and functional component of dystonia in 3 patients with both ITB pump and DBS **Authors conclusion** ITB has a role in the management of children with dystonia. ITB is beneficial in children with both primary and dystonia secondary to cerebral palsy. The benefit is subjectively greater in children with dystonia secondary to cerebral palsy, possibly due to the larger component, which is known to respond to ITB. ITB and deep brain stimulation (DBS) can be used in conjunction in children with primary dystonia.
General comments	Small sample size

Evidence Table : EFFECTIVENESS

Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	6. Ford B, Greene P, Louis ED, Petzinger G, Bressman SB, Goodman R, Brin MF, Sadiq S, Fahn S. Use of intrathecal baclofen in the treatment of patients with dystonia. Arch Neurol. 1996;53:1241-1246
Study Type / Methods	Pre- and post- intervention study. This study was conducted in Neurological Institute, Columbia-Pres-byterian Medical Center, New York, NY between March 1993 and December 1994. The aim of the study was to evaluate the effects of IT baclofen in treating patients with severe segmental or generalised dystonia. Inclusion criteria: Presence of severe dystonia and the lack of response to available oral medications at the highest tolerated doses, including oral baclofen. For spasticity of spinal origin, IT test doses of 50, 75, and 100 µg are recommended. In the patients with dystonia described in this report, a test dose that exceeded 100 µg was given if an equivocal response was observed at lower doses, provided there were no adverse effects. In 7 patients, the neurologists also used placebo injections after they explained to each patient that (1 of the next 2 or 3 injections would be saline solution). The oral medications for dystonia were not changed during the testing procedure. Videotaped examinations using a standard protocol was performed before and after the test dose injections, (for 10/13 patients who responded to IT baclofen). All videotapes were reviewed by 2 shielded investigators (B.F. and P.G.) with the use of a standard, validated dystonia rating scale. Follow-up information with regard to long term complication, IT baclofen dose requirement & complications was obtained by examining clinic charts and by patient interview. Patients, family, and caretakers were asked whether they believed the ITB treatment had continuing effectiveness. An overall global dystonia score was assigned by using a 4-point scale as follows: 0, no dystonia present; 1, mild dystonia with little impairment; 2, moderate dystonia with obvious or pronounced movements and spasms; and 3, severe dystonia preventing ambulation or the performance of daily living activities. An overall disability score was assigned by using a 4-point scale as follows: • 0, not disabled and leading a normal life • 1, mild disability but continuing full-time household duties and work outside the home • 2, moderate disability with impairment in activities of daily living but still independent • 3, severe disability with loss of independence for activities of daily living
LE	II-2
Number of Patients and Patient Characteristics	25 consecutive patients with severe generalised dystonia (n=21) or segmental dystonia (n=4) that was severe or refractory to treatment with oral medications. 4 patients with segmental dystonia: • 2 - craniofacial dystonia • 1 - brachial dystonia • 1 - truncal dystonia In addition to dystonia, • 17 (68%) had superimposed painful spasms and signs of spasticity, defined as the presence of velocity-dependent increases in tonic stretch reflexes ("clasp-knife hypertonia"), exaggerated stretch reflexes, and extensor plantar responses. • 13 had idiopathic dystonia • 7 had dystonia secondary to a diffuse encephalopathy • 5 had dystonia associated with parkinsonism • 5 individuals had undergone 1 or more previous thalamotomies for dystonia. Mean age = 35.6 years at the time of testing (range, 16 to 73 years) 13 individuals underwent pump implantation, where 11 patients were followed up more than 3 months
Intervention	Test dose: Intrathecal bolus baclofen (dose range, 25-250 µg; mean dose, 116 µg). Phase 2: Intrathecal infusion of baclofen
Comparison	7 patient placebo (saline). No comparator
Length of follow up (if applicable)	> 3 months, range 18 to 32 months, mean 21 months
Outcome measures/ Effect size	Test dose: • Based on first IT baclofen test dose, 17 (68%) of 25 patients had spasticity or painful spasms, in addition to dystonia. In 12 (70%) of these 17 patients, the test doses of IT baclofen gave clinical benefit, and 9 underwent pump implantation. By contrast, 3 (38%) of 8 patients without spasticity improved after a test injection of IT baclofen. • No significant different in the response to IT baclofen in patient with or without spasticity or pain (P = 0.13,). Post IT test dose (11 patients followed up longer than 3 months): Interview regarding continuing beneficial effect on quality of life; • 6 patients reported sustained benefit • 5 patients, IT baclofen had lost its effectiveness (2 patients – completely loss ITB efficacy) • In 9 of the 11 patients (81%) IT baclofen did not have an overall impact on a patient's overall global dystonia score or disability score, even though important aspects of the condition (e.g., pain or spasms) were helped • 5 (45%) were able to reduce or stop their previous oral medications, while 6 (54%) continued at the original doses. Baclofen dosage: In patients, who appeared to have a sustained benefit, the dose of IT baclofen was gradually increased over time. In all patients, the pump was initially programmed to deliver IT baclofen at a rate between 75 and 200 µg/d at the time of implantation. The mean peak dose of IT baclofen in patients who were followed up for more than 3 months was 1021.5 µg/d; the highest dose was 1500 µg/d. **Authors conclusion** Despite recent reports that have described the benefit in small numbers of patients with dystonia, we concluded that the role of IT baclofen in treating severe dystonia remain uncertain. Intrathecal baclofen may be more effective when dystonia is associated with spasticity or pain. In the present series we detected no significant difference in the response to IT baclofen in patients with or without spasticity or pain, perhaps owing to the small sample size.
General comments	Retrospective. Small sample size

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with dystonia?

Bibliographic Citation	1. Motta F, Stignani C, Antonello CE. Effect of intrathecal baclofen on dystonia in children with cerebral palsy and the use of functional scales. J Pediatr Orthop. 2008;28(2):213-217
Study Type / Methods	Pre- and post-intervention study. Study was conducted at the Department of Paediatric Orthopaedics at BV. Buzzi Children's Hospital, in Milan. between January 2000 and October 2005 The aim of this study was to evaluate, with the use of functional scales, the effect of ITB on generalised dystonia in 19 patients affected by CP and with severe degree of impairment. Standard video recordings were used to assess dystonia with 2 different rating scales: • The Barry-Albright Scale(BAD)-evaluates secondary dystonia in 8 regions of the body (eyes, mouth, neck, trunk, upper limbs, and lower limbs) and gives each a score from 0 to 4 • The Burke-Fahn-Marsden rating scale (BFM) - to evaluate primary dystonia but can also be used for secondary dystonia and consists of 2 sections: the movement scale, based on patient observation, and the disability scale, based on the patient's everyday activity. Inclusion criteria: • Dystonic CP • Belonging to level V of Gross Motor Function Classification System (GMFCS) • Age at implant below 18 years The patients were reassessed using the same rating scales at 3, 6, and 12 months postimplant. The surgical implant technique was modified in March 2003. Initially, the pump was positioned subcutaneously, whereas the modified technique positions the pump more deeply into the abdomen, under the external oblique muscle, and the abdominal rectus: • 14 patients subfascial technique • 5 patients subcutaneous implant technique • The catheter was positioned at level C1 for all 19 patients. Of all 19 patients: ◦ 9 were implanted with ◦ SynchroMed EI pump with a reservoir size of 10 mL, ◦ 1 patient, we used a SynchroMed EI with a reservoir size of 18 mL. ◦ 10 patients were implanted with a SynchroMed II pump with a reservoir size of 20 mL. All patients were given a subjective internal questionnaire at each follow-up: 26 questions - various aspects of the patient's life (daily activity, movement, autonomy, pain, sleeping, performance at school, communication, use and tolerance of aids, and mood) given to the patient or to the caregiver if the patient was unable to communicate.
LE	II-2
Number of Patients and Patient Characteristics	19 patients: • 13 males and 6 females, with an age at implant of between 2 years 5 months and 16 years and 6 months • Mean age was 8.49 years, (SD = 3.2 years) • All of whom had dystonia associated with CP • All 19 patients, 13 (70%) were affected by spastic / dystonic tetraplegia with severe generalised dystonia • 6 (30%) patients were affected by dystonic tetraplegia Inclusion criteria: • Dystonic CP • Belonging to level V of Gross Motor Function Classification System (GMFCS) • Age at implant below 18 years
Intervention	Intrathecal baclofen infusion • 18 patients- continuous infusion, • 1 patient - daily periodic bolus infusion
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications during follow-up period** Major complication: • 1 major complication related to catheter occurred, and it was solved by catheter replacement. Minor complication: • CSF leakage occurred in 4 of 19 patients • No data on possible influence of ITB on beginning or aggravation of scoliosis **Authors conclusion** In patients belonging to level V of Gross Motor Function Classification System and treated with ITB, a decrease in frequency and severity of dystonia is observed. The improvement eases caregiver in patient management.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	2. Motta F, Antonello CE, Stignani C. Upper limbs function after intrathecal baclofen therapy in children with secondary dystonia. J Pediatr Orthop. 2009; 29(7):817-821.
Study Type / Methods	Pre and post intervention study. Study was conducted at paediatric department at "V Buzzi" Children Hospital, Milan between January 2006 and September 2007. The aim of this study was to determine the effects of ITB therapy in patient with secondary dystonia to cerebral palsy, in addition to reducing dystonia and also improve upper limb function **Inclusion criteria** Patients whose dystonia was sufficiently severe to cause problems in performing everyday life activities, who were able to sit without support or with their seating system and to perform the tasks required by Melbourne assessment of unilateral upper limb function scale (MUUL) without wrist and elbow contractures, and who had not had botulin toxin A injection in the upper limbs in the previous 6 months before implant. Evaluation baseline and post implant: • Upper limb function assessment was conducted using MUUL • Dystonia assessment using BAD. • The preimplant assessment and the follow-ups were conducted by the same team consisting of 2 physiotherapists In all the 11 patients, the pump were positioned using the subfascial technique, the catheter was positioned at level C1.
LE	II-2
Number of Patients and Patient Characteristics	11 patient with secondary dystonia, classified as levels 3 and 4 of the Gross Motor Function Classification System: • 4 males and 7 females • 7 patients – level 3, 4 patients- level IV • Mean age at implant 11.3 years (SD ± 3.02) years
Intervention	Continuous intrathecal baclofen.
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications** • 1 catheter rupture occurred in 1 of 11 patients during the follow-up, the catheter was subsequently replaced • No drug-related complications (vomiting, headaches, respiratory depression) were reported during the study period **Authors conclusion** In patients with secondary dystonia treated with ITB, functional improvement of the upper limb limbs was observed in addition to dystonia reduction. In patients with secondary dystonia, ITB is the treatment that aims to achieve a general reduction of dystonia; this study want to show the influence that this reduction has to functional ability of patient.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with dystonia?

Bibliographic Citation	3. Albright AL, Barry MJ, Shafton DH, Ferson SS. Intrathecal baclofen for generalized dystonia. Developmental Medicine & Child Neurology. 2001;43:652-657.
Study Type / Methods	Pre and post intervention study. This study was conducted in Children Hospital of Pittsburgh, USA. The aim of the study was to evaluate the effects of intrathecal baclofen (ITB) on patients with severe generalised dystonia. Participants were evaluated between October 1993 and August 1999. Participants had dystonia that interfered with function, or comfort and had BAD scores of 3 to 4 in at least major body regions (extremities, trunk, neck). Most participants were severely developmentally and motorically delayed; Gross Motor Function Classification System levels were II in 2%, III in 2%, IV in 11%, and V in 85% of participants. Before insertion of a pump, responsiveness to ITB was usually tested. After pump implantation, participants were re-evaluated in clinic at 3, 6, 12, and 24 months using Barry-Albright Dystonia (BAD) score, then yearly for 5 years. BAD scores pretreatment were compared with scores at those time intervals using repeated measures of analysis variance (ANOVA). The present report includes patients with at least 1 year follow-up. Parents, caregivers, or participants were contacted by telephone and questioned about the effects of ITB as of September 2000.
LE	II-2
Number of Patients and Patient Characteristics	86 participants • All had generalised dystonia • Age ranged from 3 to 42 years, with a mean age of 14 years and a median of 13 years • Of the 86 participants with dystonia, 33 had coexisting spasticity, but their dystonia was the predominant movement disorder
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	5 years, median 29 months
Outcome measures/ Effect size	**Complications** Screening phase: Screening infusions were associated with side effects in 28% of cases, usually symptoms including headache, nausea, vomiting, or drowsiness. ITB therapy: • ITB infusion was associated with side effects in 26% of participants • Most common side effects was increased constipation (19%), less common were decreased neck / trunk control (8%), and drowsiness (6%) • Surgical complications occurred in 38% of participants (CSF leaks developed in 8%, infections developed in 14%, and catheter problems occurred in 21% of participants) **Authors conclusion** ITB appears to be the treatment of choice for severe generalised dystonia, particularly secondary dystonia which is inadequately treated by oral medications. Ease of care improves in 86% and function improves in one third of patients. Although approximately 8% of patients lose their responsiveness to ITB, it has been effective in the remainder for up to 7 years.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	4. Walker RH, Danisi FO, Swope DM, Goodman RR, Germano IM, Brin MF. Intrathecal baclofen for dystonia: benefits and complications during six years of experience. Movement Disorders. 2000;15(6):1242-1247.
Study Type / Methods	Pre-and post-intervention study. The study was conducted at Mount Sinai Medical Centre. Pumps were implanted between June 1993 and May 1998. Reviewed the charts of all patients. Fourteen patients with primary or secondary dystonia received intrathecal baclofen (ITB) through an implanted pump following a trial dose. Patients were selected for ITB trial if they had clinically unsatisfactory response to oral antidystonic medications, including oral baclofen. After pump implantation, the dose of ITB was increased in increments of approximately 10% until either the patient reported dose-limiting adverse effects or a dose of 1000 µg /day. Patients were rated using the Burke-Fahn Marsden (BFM) rating scale scores by a blinded rater after the dose of ITB were optimised.
LE	II-2
Number of Patients and Patient Characteristics	14 patients with dystonia: 8 had primary generalised dystonia, 1 primary cranial segmental dystonia, 5 had secondary dystonia
Intervention	Intrathecal infusion of baclofen After pump implantation, the dose of ITB was increased in increments of approximately 10% until either the patient reported dose-limiting adverse effects or a dose of 1000 µg /day
Comparison	No comparator
Length of follow up (if applicable)	Mean length therapy -29 months (range 6-64 months)
Outcome measures/ Effect size	**Complications** 6 patients had complications: • 1 patient had low volume alarm failure • 1 patient had wound breakdown at 4 weeks • 1 patient had catheter fracture • 1 patient had wound dehiscence and underperfusion • 1 patient had moderate overdose • 1 patient had catheter fracture, and underperfusion **Authors conclusion** Aetiology of dystonia did not determine the efficacy of ITB therapy, as benefit or failure was seen in both primary and secondary dystonia.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with dystonia?

Bibliographic Citation	5. Woon K, Tsegaye M, Vloeberghs MH. The role of intrathecal baclofen in the management of primary and secondary dystonia in children. Br J Neurosurg. 2007;21(4):355-358.
Study Type / Methods	Cross sectional study. The aim of this study was to review the safety and efficacy of ITB in children with dystonia. Study was conducted in University Hospital Nottingham. From October1998 to May 2006, there were 112 ITB pump implantations in 104 children with spasticity of cerebral origin. Reported the result of prospectively collected audit database. From the database, information was obtained on patients who had intrathecal baclofen pump insertion for spasticity or dystonia. The indications for ITB in dystonia were painful muscle spasms severe spasticity, and to improve deteriorating nursing care. Subsequent assessment regarding improvement in general handling and posture were undertaken by the patient's carers. Further assessments on the effectiveness of the test procedure were also made by the physiotherapists and nurses.
LE	II-3
Number of Patients and Patient Characteristics	104 children with spasticity of cerebral origin (67 males and 37 Female) Age range from 4 to 20 years Eight children (four females, four males) had ITB pump implantation for spasticity and dystonia: • Mean age of 12.5 years, range 10 to 18 years. • 1 had glutaric aciduria type 1 • 1 had Leigh' syndrome • 1 had idiopathic dystonia • 3 had panthotenate kinase associated neuronal degeneration (PKAN) • 2 had dystonia secondary to cerebral palsy • 2 had previous treatment with deep brain stimulation (DBS) • 1 who had ITB inserted, subsequently have DBS inserted
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Complications** There were four adverse events: • 2 patients had revision of the proximal catheter and remained well after their second operation • 1 patient had 1 week of postoperative pyrexia of unknown origin which settled spontaneously • 1 patient started showing signs of loss of bowel and bladder control, and hence her baclofen dose was reduced with improvement • 1 patient died due to a chest infection, septicaemia and progression of his Idiopathic dystonia (not related to the baclofen pump insertion) 3 years later. **Authors conclusion** ITB has a role in the management of children with dystonia. ITB is beneficial in children with both primary and dystonia secondary to cerebral palsy. The benefit is subjectively greater in children with dystonia secondary to cerebral palsy, possibly due to the larger component, which is known to respond to ITB. ITB and deep brain stimulation (DBS) can be used in conjunction in children with primary dystonia.
General comments	Small sample size

Evidence Table : SAFETY
Question : Is Continuous ITB infusion effective for treatment of patients with dystonia?

Bibliographic Citation	6. Ford B, Greene P, Louis ED, Petzinger G, Bressman SB, Goodman R, Brin MF, Sadiq S, Fahn S. Use of intrathecal baclofen in the treatment of patients with dystonia. Arch Neurol. 1996;53:1241-1246
Study Type / Methods	Pre- and post- intervention study. This study was conducted in Neurological Institute, Columbia-Pres-byterian Medical Center, New York, NY between March 1993 and December 1994. The aim of the study was to evaluate the effects of IT baclofen in treating patients with severe segmental or generalised dystonia. Inclusion criteria: Presence of severe dystonia and the lack of response to available oral medications at the highest tolerated doses, including oral baclofen. For spasticity of spinal origin, IT test doses of 50, 75, and 100 µg are recommended. In the patients with dystonia described in this report, a test dose that exceeded 100 µg was given if an equivocal response was observed at lower doses, provided there were no adverse effects. In 7 patients, the neurologists also used placebo injections after they explained to each patient that (1 of the next 2 or 3 injections would be saline solution). The oral medications for dystonia were not changed during the testing procedure. Videotaped examinations using a standard protocol was performed before and after the test dose injections, (for 10/13 patients who responded to IT baclofen). All videotapes were reviewed by 2 shielded investigators (B.F. and P.G.) with the use of a standard, validated dystonia rating scale. Follow-up information with regard to long term complication, IT baclofen dose requirement & complications was obtained by examining clinic charts and by patient interview. Patients, family, and caretakers were asked whether they believed the ITB treatment had continuing effectiveness. An overall global dystonia score was assigned by using a 4-point scale as follows: 0, no dystonia present; 1, mild dystonia with little impairment; 2, moderate dystonia with obvious or pronounced movements and spasms; and 3, severe dystonia preventing ambulation or the performance of daily living activities. An overall disability score was assigned by using a 4-point scale as follows: • 0, not disabled and leading a normal life; • 1, mild disability but continuing full-time household duties and work outside the home; • 2, moderate disability with impairment in activities of daily living but still independent; • 3, severe disability with loss of independence for activities of daily living
LE	II-2
Number of Patients and Patient Characteristics	25 consecutive patients with severe generalised dystonia (n=21) or segmental dystonia (n=4) that was severe or refractory to treatment with oral medications. 4 patients with segmental dystonia: • 2 - craniofacial dystonia • 1 - brachial dystonia • 1 - truncal dystonia In addition to dystonia, • 17 (68%) had superimposed painful spasms and signs of spasticity, defined as the presence of velocity-dependent increases in tonic stretch reflexes ("clasp-knife hypertonia"), exaggerated stretch reflexes, and extensorplantar responses. • 13 had idiopathic dystonia • 7 had dystonia secondary to a diffuse encephalopathy • 5 had dystonia associated with parkinsonism • 5 individuals had undergone 1 or more previous thalamotomies for dystonia. Mean age = 35.6 years at the time of testing (range, 16 to 73 years) 13 individuals underwent pump implantation, where 11 patients were followed up more than 3 months
Intervention	Test dose: Intrathecal bolus baclofen (dose range, 25-250 µg; mean dose, 116 µg). Phase 2: Intrathecal infusion of baclofen
Comparison	7 patient placebo (saline). No comparator
Length of follow up (if applicable)	> 3 months, range 18 to 32 months, mean 21 months
Outcome measures/ Effect size	**Complications** Bolus test dose: • 18 patients had mild reversible side effects including drowsiness, leg numbness, weakness, headache, and light-headedness • 2 patients experienced respiratory depression that required oxygen by mask and observation in the intensive care unit;1 of these individuals had received a dose of 125 µg after experiencing mild drowsiness following an injection of IT baclofen (75 µg) and intravenous diazepam (20 mg) given 1 day earlier. The other patient experienced respiratory depression after receiving a dose of 200 µg; a bolus injection of 150 µg 1 day earlier had given some benefit with no side effects. • The overall complication rate was 20.5% for doses below or equal to 100 µg, and it was 46% for doses that exceeded 100 µg—a significant difference [P < 0.03; OR, 3.19 (95% CI 1.10 to 9.32)]. Long term IT baclofen treatment: • 2 patients developed cerebrospinal fluid leaks and spinal headaches, requiring blood patches • 5 (38%) of the 13 patients with implantable pumps have experienced severe complications, all requiring hospitalisation: baclofen overdose with respiratory depression (n = 4), baclofen withdrawal (n = 1), fibrosis at the catheter tip that required replacement (n = 1), skin erosion that required pump removal (n = 1). **Authors conclusion** Despite recent reports that have described the benefit in small numbers of patients with dystonia, we concluded that the role of IT baclofen in treating severe dystonia remain uncertain. Intrathecal baclofen may be more effective when dystonia is associated with spasticity or pain. In the present series we detected no significant difference in the response to IT baclofen in patients with or without spasticity or pain, perhaps owing to the small sample size.
General comments	Retrospective. Small sample size

SPASTICITY AND / OR DYSTONIA
Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	1. Uchiyama T, Nakanishi K, Fukawa N, Yoshioka H, Murakami S, Nakano N, Kato A. Neoromodulation using intrathecal therapy for spasticity and dystonia. Neurol Med Chir. 2012;52:463-469
Study Type / Methods	Pre and post intervention study conducted at Department of Neurosurgery, Kinki University faculty of Medicine, Osaka-sayama, Osaka Osaka Japan. Aim of the study was to report the surgical methods and therapeutic outcomes of 22 spastic and dystonic patients who underwent ITB therapy, together with an investigation of effects on metabolic and respiratory functions. The study included 22 patients who exhibited diffuse spasticity or dystonia. If the main symptoms were located in the spastic lower limbs, the intrathecal catheter was placed at the lower thoracic spine level (T10-T12). In case of spastic tetraplegia and generalised dystonia, the catheters were placed at the cervical spine level (C1-C2). Surgical response was determined by measuring the Ashworth score of the affected limbs before and 6 months after the procedure. Respiratory gas analyser was used to measure resting metabolic rate before and 1 month after the procedure in the most recent 10 patients who underwent ITB therapy. Effects on respiratory function were also measured and evaluated in the same 10 patients using polysomnography before and 1 month after the procedure.
LE	II-2
Number of Patients and Patient Characteristics	22 patients: • 14 males, 8 females • Age range, 20 to 64 years • Underlying pathology was intractable spasticity in 19 patients, and secondary generalised dystonia in 3 patients
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	Mean duration of follow-up was 25 months (range, 6 – 53.8 months)
Outcome measures/ Effect size	**Changes in Pre and Post ITB treatment** **Mean Ashworth Scale score before and 6 months after procedure** • Lower limbs: ◦ Mean Ashworth score for the affected lower limbs when the intrathecal catheter was placed at the lower thoracic spine level improved significantly from 3.07 to 1.69, $P < 0.0001$ ◦ Mean Ashworth score for the affected lower limbs when the intrathecal catheter was placed at the cervical spine level in tetraplegia and dystonic patients improved significantly from 3.68 to 2.62, $P < 0.0001$ Lower limbs spasticity exhibited highly significant improvement regardless of catheter position. • Upper limbs: ◦ Mean Ashworth score for the affected upper limbs when the intrathecal catheter was placed at the lower thoracic spine level improved significantly from 2.87 to 2.30, $P < 0.004$ ◦ Mean Ashworth score for the affected upper limbs when the intrathecal catheter was placed at the cervical spine level in tetraplegia and dystonic patients improved significantly from 2.72 to 1.88, $P < 0.0001$ Upper limbs spasticity exhibited more significant improvement when catheter was placed at the cervical spine. • Standardised resting metabolic rate before and 1 month after procedure: ◦ Resting hypermetabolism declined after the procedure ◦ Reduction was particularly marked in patients with dystonia and cerebral palsy, for whom metabolic rate had been over 1.5 times the normal value before surgery • Apnea-hypopnea index (AHI) per hour of sleep before and 1 month after procedure: ◦ Before the procedure the AHI was normal (AHI, 0-4) in 3 patients, mild (AHI 5-14) in 4 patients, moderate (AHI 15-30) in 2 patients and severe (AHI > 31). The 3 patients with severe or moderate AHI score improved markedly, whereas 4 of 7 patients with normal or mild scores showed improvement, and no change was seen in the 3 remaining patients. ◦ Sleep apnea thus improved or remained unchanged in all cases, and did not worsen in any patient
General comments	Small sample size

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	2. Motta F, Antonello C, Stignani C. Intrathecal baclofen and motor function in cerebral palsy. Developmental Medicine & Child Neuroloy. 2011;53:443-448
Study Type / Methods	Pre and post intervention study conducted at the Department of Paediatric Orthopaedics, 'V Buzzi' Childrens Hospital, Milan, Italy. Aim of the study was to determine the impact of intrathecal baclofen (ITB) therapy on motor function in patients with spastic and dystonic cerebral palsy (CP). Studied 37 patients with CP treated with intrathecal baclofen(ITB). Eighteen patients were affected by spastic diplegia, 12 by spastic quadriplegia, six by dystonic quadriplegia, and one by hemidystonia. Motor function was assessed by the Gross Motor Function Measure (GMFM) before treatment and 12 months after treatment. In patients with spastic CP, spasticity were assessed before the implant and at follow-up visit by means of Ashworth scale. A standard video recording was used to assess dystonia by Barry-Albright Dystonia (BAD) scale in patients with dystonic CP. The GMFM consists of 88 items grouped into 5 dimensions: (A) lying & rolling; (B) sitting; (C) crawling & kneeling; (D) standing; (E) walking, running & jumping. Data were collected retrospectively for patients treated before 2008, whereas for patients treated after 2008 data were collected prospectively during the follow-up visits scheduled according to the clinical practice. A subjective questionnaire aimed at identifying changes in patients abilities after the implant was administered to each child or caregiver. The questionnaire investigated patient's improvements in transfer, self-care, seat position, endurance, and walking.
LE	II-2
Number of Patients and Patient Characteristics	37 patients: • 18 males, 19 females • Age at implant ranging from 4 to 29 years (mean 13 year 7 months, SD 7 year) • 30 patients affected by spastic CP: Mean age, 13 years 1 month (SD, 6 years) • 7 patients affected by dystonic CP: Mean age, 13 years 1 month (SD, 6 years) • At baseline; nine participants were in Gross Motor Function Classification System (GMFCS) level II, 13 in level III, seven in level IV, and 8 in level V.
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Changes in Pre and Post ITB treatment** **Gross Motor Function Measure (GMFM) percentage scores before and after ITB** • Overall population (N=37 patients), Median (IQR): ◦ Statistically significant improvement in the total GMFM score, 65.66 (49.61) before ITB compared with 70.33 (43.86) at 12 months after ITB, P = 0.004 ◦ Statistically significant improvement in each dimension (P < 0.05, except for standing (Dimension D) **GMFM percentage scores before and after ITB** • Assessed by degrees of impairment, Median (IQR): ◦ Statistically significant improvement in the total GMFM score in patients with mild-moderate impairment; 73.39 (14.79) before ITB compared with 76.71 (9.35) at 12 months after ITB, P = 0.033 ◦ Statistically significant improvement in the total GMFM score in patients with severe impairment; 21.73 (21.49) before ITB compared with 25.47 (19.94) at 12 months after ITB, P = 0.008 **GMFM percentage scores before and after ITB** • Analysis by age, Median (IQR): ◦ Statistically significant improvement in the total GMFM score in patients < 8 years; 23.04 (32.68) before ITB compared with 29.13 (32.30) at 12 months after ITB, P = 0.007 ◦ Statistically significant improvement in the total GMFM score in patients 8 to 18 years; 67.82 (29.15) before ITB compared with 70.77 (25.62) at 12 months after ITB, P = 0.018 ◦ Improvement in the total GMFM score in patients > 18 years; 73.63 (14.95) before ITB compared with 76.90 (7.08) at 12 months after ITB (not significant) • Ashworth scale score, Median (IQR): ◦ In patients with spasticity, Ashworth scale score decreased from a median of 3 (IQR 1) before the implant to a median value of 2 (IQR 1) at 12 months after the implant, (P < 0.001) • BAD scale score, Median (IQR): ◦ In patients with dystonia, BAD scale score decreased form a median of 21 (IQR 10) before the implant to a median value of 15 (IQR 4) at 12 months after the implant, (P = 0.018) **Subjective questionnaire:** 24 patients reported an improvement in transfer, 30 in care management, 25 in seat position, 31 in endurance, and 25 in walking None of the assessed patients / caregivers reported worsening in the evaluated performance For the overall subjective evaluation of the ITB therapy, 35 patients were satisfied whereas two were undecided **Authors conclusion** The results suggest that ITB therapy is an effective treatment for managing spasticity and dystonia, and for improving motor function in children with CP.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	3. Ward A, Hayden S, Dexter M, Scheinberg A. Continuous intrathecal baclofen for children with spasticity and/or dystonia: Goal attainment and complications associated with treatment. Journal of Paediatrics and Child Health. 2009;45:720-726
Study Type / Methods	Pre and post intervention study of goal attainment after ITB therapy and retrospective review of medical records for complications conducted in Australia. Aim of the study was to describe complications of intrathecal baclofen (ITB) therapy in children with spasticity and/or dystonia. Eligibility for ITB therapy was determined by a routine clinical workup, including being of a size sufficient to receive the pump (generally greater than 15 kg), and having a positive response to a bolus test dose. The children were described as dystonia-predominant or spasticity-predominant and the subgroups were compared. Goals were assessed at baseline and goal attainment at 6 months post-implant. Data were analysed using Wilcoxon signed-rank test. The patients' goals were measured with the Canadian Occupational Performance Measure (COPM) and goal attainment scaling (GAS). The GAS scores were converted to normalised T-scores and the subjects who achieved a GAS T-score > 50 were deemed to have achieved their goals. The study ran from 1999 to 2007.For the COPM, a change in score of two or more was considered clinically significant. Complication rates were calculated by dividing the number of complications by the duration of pump implantation.
LE	II-2
Number of Patients and Patient Characteristics	25 children: • 10 males, 15 females • Mean age at 1st implant was 10 years 3 months (SD, 3 years 5 months) • 88% had CP (nine dystonia- predominant / 12 spasticity predominant), 4 had other diagnoses leading to spasticity or dystonia • 71% were GMFCS level V, 21% level IV, and 8% level III
Intervention	Intrathecal infusion of baclofen. SynchroMed EL and II Infusion Systems (Medtronic Neurological, Minneapolis, MN)
Comparison	No comparator
Length of follow up (if applicable)	Minimum follow-up period of 8 months (range, 0.66 years to 7.94 years)
Outcome measures/ Effect size	**Goal attainment** Overall, 16 subjects had full data set with assessment of goals at baseline and goal attainment at 6 months post-implant. Twelve were GMFCS level V, two were level IV, and one was level III. • Canadian Occupational Performance Measure (COPM) –satisfaction domain, Median [interquartile (IQR) ranges]: ◦ Statistically significant increase in the satisfaction domain of COPM was demonstrated 6 months after implantation of baclofen pump, 2.1 (1.76 to 2.75) at baseline compared with 5.9 (4.86 to 7.05) at 6 months, difference 3.5(2.40 to 5.20), $P < 0.001$ ◦ Statistically significant increase in the performance domain of COPM was demonstrated 6 months after implantation of baclofen pump, 2.2 (2.00 to 2.70) at baseline compared with 5.4 (4.6 to 6.9) at 6 months, difference 3.0 (2.20 to 4.50), $P < 0.001$ • Goal attainment scaling (GAS) T-score, Median [interquartile (IQR) ranges]: ◦ Statistically higher at 6 months after implantation of baclofen pump, 35 at baseline compared with 56 (47 to 65) at 6 months, difference 21(12-30), $P < 0.001$ ◦ 70% of subjects attained their goals, having achieved a GAS score of 50 or over at 6 months **Muscle tone** • Modified Ashworth scale score, Median: ◦ Significant reduction in muscle tone, median score change from 2.28 to 1.43, $P < 0.05$ **Dystonia** • BAD scale score, Median: ◦ A reduction from an average 28.67 to 15.75, greater than 25% improvement considered to be significant for this measurement tool **Authors conclusion** ITB results in statistically significant levels of satisfaction and goal attainment in children with spasticity and / or dystonia. GAS was a useful measure of goal attainment. While ITB is effective for children and dystonia, those with dystonia have a higher rate of complications.
General comments	

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	4. Tasseel Ponche S, Ferrapie AL, Chenet A, Menei P, Gambart G, Menegalli Bogeli D, Perrouin Verbe B, Gay S, Richard I. Intrathecal baclofen in cerebral palsy. A retrospective study of 25 wheelchair-assisted adults. Annals of Physical and Rehabilitation Medicine. 2010;53:483-498
Study Type / Methods	Pre and post intervention studies conducted at three cities in western French (Angers, Le Mans and Nantes). Aim of the study was to describe the long-term efficacy of ITB in 25 wheelchair-assisted adults with cerebral palsy (CP) in terms of impairments, activity limitation, participation restriction and quality of life. The secondary objectives were to assess drug safety and to evaluate satisfaction with ITB. A retrospective analysis and clinical examination of 25 wheelchair-assisted adults with cerebral palsy receiving ITB initiated between 1999 and 2009 in three different cities in Western France. Inclusion criteria: • A diagnosis of CP • Complete wheelchair dependent • Age > 15 at the time of pump implantation All patients were seen again between June 2008 and June 2009 for the observational evaluation of spasticity on the Ashworth scale. The efficacy of ITB was subjectively assessed in a questionnaire. Measures satisfaction on visual analog scale (VAS). The pretherapeutic objectives were achieved when the patients reported improvement of more than 5 out of 10 the VAS.
LE	II-2
Number of Patients and Patient Characteristics	25 wheelchair assisted adult CP patients: • 14 men, 11 women • Mean age ± SD = 29.6 ± 12.66 years • 84% bilateral spastic CP, 16% choreoathetotic CP • 76% of patients were dependent for maneuvering their wheelchair • 28% were able to answer the questionnaire unaided
Intervention	Intrathecal infusion of baclofen. Programmable pump (Medtronic SynchroMed II devices)
Comparison	No comparator
Length of follow up (if applicable)	Total number of years of follow-up was 116 (for 25 patients)
Outcome measures/ Effect size	Efficacy of continuous intrathecal infusion of baclofen (differences between baseline and after therapy) Clinical efficacy • Modified Ashworth scale score [Mean± SD]: ◦ Decreased from 3.2 ± 0.4 points (range, 3 to 4) before initiation of therapy to 2.0 ± 0.6 points (range, 1 to 4) after therapy Functional efficacy • Subjective satisfaction scale (VAS) ◦ In terms of main objectives set prior to implantation, 96% of patients were seeking facilitated nursing and the mean satisfaction score was 6 ± 3.3 (range, 0 to 10) ◦ 88% of patients were seeking improved wheelchair comfort and the mean score was 6 ± 3 (range, 0 to 9) ◦ 24% of patients wanted a decrease in abnormal choreothetotic movement and the mean score was 3 ± 4.1 (range, 0 to 8) ◦ The objectives were not at all reached (VAS score = 0 out of 10) for 3 patients and clearly reached (VAS score = 7 or 8 out of 10) for two patients ◦ in all, 80% of the patients considered that their main ITB objectives has been achieved (VAS score greater than 5 out of 10) ◦ 88% of patients experienced improvement other than those wished for in the treatment objectives: pain relief in 68% (15/22) cases, easier movement execution in 45% of cases (10/22) and better sleep in 23% of cases (5/22) ◦ 72% reported better quality of life (VAS score greater than 5 out of 10) ◦ Overall ITB satisfaction score was reported 7 ± 3.2, with 80% of satisfied patients (VAS satisfaction score greater than 5 out of 10) **Authors conclusion** Wider use of ITB in this indication is likely and should lead to a better understanding of the drug's pharmacological effects on motor disorders and pain. Use of Goal attainment Assessment Scale or Caregiver Questionnaire can help us.
General comments	Retrospective analysis

Evidence Table : EFFECTIVENESS
Question : Is Continuous ITB infusion effective for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	5. Meythaler JM, Guin-Renfroe S, Grabb P, Hadley MN. The long-term continuous infused intrathecal baclofen for spastic – dystonic hypertonia in traumatic brain injury:1–year experience. Arch Phys Med Rehabil.1999;80:13-19
Study Type / Methods	Pre and post intervention study at tertiary care outpatient and inpatient rehabilitation centre directly attached to a university hospital, Birmingham, Alabama. Aim of the study was to determine if the long-term use of continuously infused intrathecal baclofen (ITB) over a 1-year period will control spastic-dystonic hypertonia in patients with traumatic brain injury (TBI). Inclusion criteria: • Between 10 and 75 years of age • Diagnosed with severe spastic / dystonic hypertonia in the lower extremities of at least 6 months duration • Failed to respond satisfactorily to treatment with oral antispasticity medications or had experienced unacceptable side effects at effective treatment dosages TBI patients were admitted to the study after screening via a bolus injection of either intrathecal normal saline or 50 µg of baclofen. Data for Ashworth rigidity scores, spasm scores, and deep tendon reflex scores were collected for both the upper extremities (UE) and lower extremities (LE). Patients whose LE Ashworth scores decreased an average of 2 points were then offered implantation of a computer-controlled pump for continuous ITB. Changes over time were assessed statistically via Friedman's analysis for ordinal data and ANOVA for linear data. Differences between set points in time were also assess via Wilcoxon signed rank.
LE	II-2
Number of Patients and Patient Characteristics	17 patients with acquired brain injury: • 14 men, 3 women • Age range between 10 and 55 years of age (average, 25 years) • All had severe spasticity and dystonia that interfered with their activities of daily living • Initial injuries had occurred 6 months or longer before the study, and all patients were recruited consecutively
Intervention	Intrathecal infusion of baclofen. Programmable pump
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	Efficacy of continuous intrathecal infusion of baclofen (differences between baseline and after 1 year of treatment) Lower extremities • Average lower extremities Ashworth score (Mean ± SD) ◦ Decreased 2.2 points from 3.5 ± 1.3 points before treatment to 1.7 ± 0.9 points after 1 year of treatment, P < 0.0001 • Average lower extremities reflex score (Mean ± SD) ◦ Decreased 2.4 points from 2.5 ± 1.1 points before treatment to 0.1 ± 0.3 points after 1 year of treatment, P < 0.0001 • Average lower extremities spasm frequency score (Mean ± SD) ◦ Decreased 1.6 points from 1.8 ± 1.3 points before treatment to 0.2 ± 0.5 points after 1 year of treatment, P< 0.0001 Upper extremities: • Average upper extremities Ashworth score (Mean ± SD) ◦ Decreased 1.4 points from 2.9 ± 1.5 points before treatment to 1.6 ± 1.0 points after 1 year of treatment, P < 0.0001 • Biceps reflex score (Mean ± SD) ◦ Decreased1.2 points from 2.2 ± 0.5 points before treatment to 1.0 ± 0.8 points after 1 year of treatment, P < 0.0001 • Average upper extremities spasm frequency score (Mean ± SD) ◦ Decreased 1.0 points from 1.2 ± 1.5 points before treatment to 0.2 ± 0.6 points after 1 year of treatment, P< 0.0001 Dosage: At the end of 1 year of treatment, the average dosage of ITB to achieve this reduction was 301 µg ± 150 (range; 120 to 675 ug/day) **Authors conclusion** Continuous intrathecal infusion of baclofen is capable of maintaining a reduction in spasticity and dystonia in both the upper and lower extremities of TBI patients.
General comments	Industry sponsored

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	1. Uchiyama T, Nakanishi K, Fukawa N, Yoshioka H, Murakami S, Nakano N, Kato A. Neoromodulation using intrathecal therapy for spasticity and dystonia. Neurol Med Chir. 2012;52:463-469
Study Type / Methods	Pre and post intervention study conducted at Department of Neurosurgery, Kinki University faculty of Medicine, Osaka-sayama, Osaka Japan. Aim of the study was to report the surgical methods and therapeutic outcomes of 22 spastic and dystonic patients who underwent ITB therapy, together with an investigation of effects on metabolic and respiratory functions. The study included 22 patients who exhibited diffuse spasticity or dystonia. If the main symptoms were located in the spastic lower limbs, the intrathecal catheter was placed at the lower thoracic spine level (T10-T12). In case of spastic tetraplegia and generalised dystonia, the catheters were placed at the cervical spine level (C1-C2). Surgical response was determined by measuring the Ashworth score of the affected limbs before and 6 months after the procedure. Respiratory gas analyser was used to measure resting metabolic rate before and 1 month after the procedure in the most recent 10 patients who underwent ITB therapy. Effects on respiratory function were also measured and evaluated in the same 10 patients using polysomnography before and 1 month after the procedure.
LE	II-2
Number of Patients and Patient Characteristics	22 patients: • 14 males, 8 females • Age range, 20 to 64 years • Underlying pathology was intractable spasticity in 19 patients, and secondary generalised dystonia in 3 patients
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	Mean duration of follow-up was 25 months (range, 6 – 53.8 months)
Outcome measures/ Effect size	**Complications** Complications included catheter displacement in 2 patients, catheter fracture in 1 patient, and pump infection in 1 patient
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	2. Motta F, Antonello C, Stignani C. Intrathecal baclofen and motor function in cerebral palsy. Developmental Medicine & Child Neuroloy.2011; 53:443-448
Study Type / Methods	Pre and post intervention study conducted at the Department of Paediatric Orthopaedics, 'V Buzzi' Childrens Hospital, Milan, Italy. Aim of the study was to determine the impact of intrathecal baclofen (ITB) therapy on motor function in patients with spastic and dystonic cerebral palsy (CP). Studied 37 patients with CP treated with intrathecal baclofen(ITB). Eighteen patients were affected by spastic diplegia, 12 by spastic quadriplegia, six by dystonic quadriplegia, and one by hemidystonia. Motor function was assessed by the Gross Motor Function Measure (GMFM) before treatment and 12 months after treatment. In patients with spastic CP, spasticity were assessed before the implant and at follow-up visit by means of Ashworth scale. A standard video recording was used to assess dystonia by Barry-Albright Dystonia (BAD) scale in patients with dystonic CP. The GMFM consists of 88 items grouped into 5 dimensions: (A) lying & rolling; (B) sitting; (C) crawling & kneeling; (D) standing; (E) walking, running & jumping. Data were collected retrospectively for patients treated before 2008, whereas for patients treated after 2008 data were collected prospectively during the follow-up visits scheduled according to the clinical practice. A subjective questionnaire aimed at identifying changes in patients abilities after the implant was administered to each child or caregiver. The questionnaire investigated patients' improvements in transfer, self-care, seat position, endurance, and walking.
LE	II-2
Number of Patients and Patient Characteristics	37 patients: • 18 males, 19 females • Age at implant ranging from 4 to 29 years (mean 13 year 7 months, SD 7 year) • 30 patients affected by spastic CP: Mean age, 13 years 1 month (SD, 6 years) • 7 patients affected by dystonic CP: Mean age, 13 years 1 month (SD, 6 years) At baseline; nine participants were in Gross Motor Function Classification System (GMFCS) level II, 13 in level III, seven in level IV, and 8 in level V
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	12 months
Outcome measures/ Effect size	**Complications** During the follow-up major complications occurred in four patients: three were catheter related and the catheter was subsequently replaced. Infection occurred in one patient which was resolved with antibiotic treatment. Leakage of cerebrospinal fluid occurred only in 1 patient, which cleared up spontaneously. No drug related complications were reported. **Authors conclusion** The results suggest that ITB therapy is an effective treatment for managing spasticity and dystonia, and for improving motor function in children with CP.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	3. Ward A, Hayden S, Dexter M, Scheinberg A. Continuous intrathecal baclofen for children with spasticity and/or dystonia: Goal attainment and complications associated with treatment. Journal of Paediatrics and Child Health. 2009;45:720-726
Study Type / Methods	Pre and post intervention study of goal attainment after ITB therapy and retrospective review of medical records for complications conducted in Australia. Aim of the study was to describe complications of intrathecal baclofen (ITB) therapy in children with spasticity and/or dystonia. Eligibility for ITB therapy was determined by a routine clinical workup, including being of a size sufficient to receive the pump (generally greater than 15 kg), and having a positive response to a bolus test dose. The children were described as dystonia-predominant or spasticity-predominant and the subgroups were compared. Goals were assessed at baseline and goal attainment at 6 months post-implant. Data were analysed using Wilcoxon signed-rank test. The patients' goals were measured with the Canadian Occupational Performance Measure (COPM) and goal attainment scaling (GAS). The GAS scores were converted to normalised T-scores and the subjects who achieved a GAS T-score > 50 were deemed to have achieved their goals. The study ran from 1999 to 2007.For the COPM, a change in score of two or more was considered clinically significant. Complication rates were calculated by dividing the number of complications by the duration of pump implantation.
LE	II-2
Number of Patients and Patient Characteristics	25 children: • 10 males, 15 females • Mean age at 1st implant was 10 years 3 months (SD, 3 years 5 months) • 88% had CP (nine dystonia- predominant / 12 spasticity predominant), 4 had other diagnoses leading to spasticity or dystonia • 71% were GMFCS level V, 21% level IV, and 8% level III
Intervention	Intrathecal infusion of baclofen. SynchroMed EL and II Infusion Systems (Medtronic Neurological Minneapolis, MN)
Comparison	No comparator
Length of follow up (if applicable)	Minimum follow-up period of 8 months (range, 0.66 years to 7.94 years)
Outcome measures/ Effect size	**Complications** • Complication rate was 0.38 per year of pump operation, higher in subjects with dystonia (0.71) compared with those with spasticity (0.25), difference 0.46, (P = 0.0017) • Risk ratio of complication in children with dystonia compared with children with spasticity was 2.85 (CI: 1.36 to 6.08), P < 0.0034 • In the spasticity predominant group, CSF leak was the most common problem at 27% (rate, 0.06 pump years) followed by infection and baclofen withdrawal (13% or a rate of 0.03 pump years each) • In the dystonia-predominant group, infection was the most common at 22% (rate 0.16 pump years), followed by pump erosion (17%; rate of 0.12 pump years). There were high rates (0.08 per pump years of procedure complications, catheter occlusions and excessive frequency of refills. Cather problems were 4 times more likely in the dystonic group (rate of 0.12 per pump years compared with the spastic group (rate of 0.03 per pump year). • Almost 50% of total complications occurred in the nine patients with dystonia **Authors conclusion** ITB results in statistically significant levels of satisfaction and goal attainment in children and spasticity and / or dystonia. GAS was a useful measure of goal attainment. While ITB is effective for children and dystonia, those with dystonia have a higher rate of complications.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	4. Tasseel Ponche S, Ferrapie AL, Chenet A, Menei P, Gambart G, Menegalli Bogeli D, Perrouin Verbe B, Gay S, Richard I. Intrathecal baclofen in cerebral palsy. A retrospective study of 25 wheelchair-assisted adults. Annals of Physical and Rehabilitation Medicine. 2010;53:483-498
Study Type / Methods	Pre and post intervention studies conducted at three cities in western French (Angers, Le Mans and Nantes). Aim of the study was to describe the long-term efficacy of ITB in 25 wheelchair-assisted adults with cerebral palsy (CP) in terms of impairments, activity limitation, participation restriction and quality of life. The secondary objectives were to assess drug safety and to evaluate satisfaction with ITB. A retrospective analysis and clinical examination of 25 wheelchair-assisted adults with cerebral palsy receiving ITB initiated between 1999 and 2009 in three different cities in Western France. Inclusion criteria: • A diagnosis of CP • Complete wheelchair dependent • Age > 15 at the time of pump implantation All patients were seen again between June 2008 and June 2009 for the observational evaluation of spasticity on the Ashworth scale. The efficacy of ITB was subjectively assessed in a questionnaire. Measures satisfaction on visual analog scale (VAS). The pretherapeutic objectives were achieved when the patients reported improvement of more than 5 out of 10 the VAS.
LE	II-2
Number of Patients and Patient Characteristics	25 wheelchair assisted adult CP patients: • 14 men • 11 women • Mean age ± SD = 29.6 ± 12.66 years • 84% bilateral spastic CP, 16% choreoathetotic CP • 76% of patients were dependent for maneuvering their wheelchair • 28% were able to answer the questionnaire unaided Inclusion criteria: • A diagnosis of CP • complete wheelchair dependent • age > 15 at the time of pump implantation
Intervention	Intrathecal infusion of baclofen. Programmable pump (Medtronic SynchroMed II devices)
Comparison	No comparator
Length of follow up (if applicable)	Total number of years of follow-up was 116 (for 25 patients)
Outcome measures/ Effect size	**Complications and adverse events** Complications occurred in 32% of the patients, with an overall rate of 0.07 complications / pump-year and transient interruption of the treatment or surgical removal of the ITB pump was necessary in 16% of cases **Authors conclusion** Wider use of ITB in this indication is likely and should lead to a better understanding of the drug's pharmacological effects on motor disorders and pain. Use of Goal attainment Assessment Scale or Caregiver Questionnaire can help us.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	5. Dickey MP, Rice M, Kinnet DG, Lambert R, Donauer S, Gerber MA, Staat MA. Infectious complications of intrathecal baclofen pump devices in a paediatric population. The Paediatric Infectious Disease Journal. 2013;32(7):715-722
Study Type / Methods	Cross sectional study at Cincinnati Children's Hospital Medical Centre (CCHMC), Cincinnati. Aim of the study was to determine the proportion of patients with infectious complications of ITB therapy, identify risk factors associated with infections in children with ITB pump devices and describe the clinical presentations, treatment and outcomes of ITB infection in a paediatric population over a 15 year time period. Patients who had an initial ITB implanted at Cincinnati Children's Hospital Medical Centre (CCHMC) were followed to determine the proportions of patients with infectious and non infectious complications identify risk factors for infection and describe the clinical presentations, treatment and outcomes of infectious complications. A review of patients medical record was performed to collect demographic and clinical data on ITB device-associated surgical procedures, ITB complications, microbial culture results, antimicrobial treatment and outcomes.
LE	II-3
Number of Patients and Patient Characteristics	139 patients: • 62% males, 38% females • Mean age at the time of the initial device implantation was 13.6 years (range, 6 months to 41 years) • Majority of patients were 21 years of age or younger at the time of ITB implantation • Site of ITB device implantation was subfascial in 77 patients (55%) and subcutaneous in 62 (45%) • Secondary spasticity / dystonia
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	Minimum 1 year follow-up
Outcome measures/ Effect size	**Complications** • In the first year of follow-up, 83% had no complications or secondary procedures, 17% had at least 1 secondary procedure and 5% had an infectious complication • The median time until infection was 14 days (mean 33 ± 42 days) • Patients with secondary spasticity or dystonia from traumatic brain injury were more likely to have infections than patients with cerebral palsy (86% versus 14%, $P < 0.0001$) • In 94 patients with a first secondary procedure, 29% had at least l other procedure and 8% had an infection in the 1 year follow-up • Overall, 24 patients had 27 ITB device associated infections (10 after initial implantation and1 7 after secondary ITB procedures). There were 2% superficial infections, 33% deep infections and 45% organ space infections. • Staphylococcus aureus was isolated in 50% of those cultures obtained • Explantation was required in 59% of patients with an infection and differed by infection type: superficial (17%), deep (44%) and organ space (92%), $P = 0.004$ **Authors conclusion** Infectious complications were relatively uncommon; however, when present, frequently led to the explanation of the ITB pump device.
General comments	

Evidence Table : SAFETY
Question : Is Continuous ITB infusion safe for treatment of patients with spasticity and / or dystonia?

Bibliographic Citation	6. Burn SC, Zeller R, Drake JM. Do baclofen pumps influence the development of scoliosis in children? J Neurosurg Pediatrics. 2010;5:195-199
Study Type / Methods	Cross sectional study conducted at Toronto, Ontario. Aim of the study was to assess the incidence of scoliosis. Case notes and radiological studies were reviewed at two different sites: the acute paediatric hospital where surgery and initial follow-up are performed and the rehabilitation centre where spasticity clinic is held. Information was gathered by 3 investigators and tabulated on a data collection tool. Cobb angles were measured on pre and post operative 3 ft spine radiographs, coronal chest radiographs (standing when possible), and on abdominal radiographs by a radiologist or neurosurgeon. Mean Cobb angle progression per year was calculated. All other causes of progressive scoliosis were excluded.
LE	II-3
Number of Patients and Patient Characteristics	32 patients: • Diagnosis were as follows: ◦ spastic cerebral palsy (16), dystonic cerebral palsy (7), hypoxic injury/head injury / cerebrovascular accident (4), others (5) • Mean age at pump insertion was 10.6 years (range, 4 to 17 years) • Male /female ratio was 25:13
Intervention	Intrathecal infusion of baclofen
Comparison	No comparator
Length of follow up (if applicable)	Mean follow-up period was 31 months (range, 1 to 118 months)
Outcome measures/ Effect size	Scoliosis progression / per year • Mean annual progression in Cobb angle in the entire group was 18.43° (range 0 to 67.68°, median 12.13°) • Mean annual Cobb angle progression was similar in all 4 subgroups : cerebral palsy, cerebral palsy / dystonia, head injury, others (range; 15.54° to 20.27°) • Analysis of curve progression before and after growth spurt showed a greater rate of curve progression in patients with pumps inserted before the age of 15 years. Cobb angle progression (° / yr), Mean ± SD: < 15 years (20° ± 20° /yr), ≥ 15 years (12°± 9° /yr **Authors conclusion** In the authors group of patients there was notable development and progression of scoliosis at a greater than previously reported rate for the same patient population, and also greater than previously reported patients with intrathecal baclofen pumps. The largest possible confounding factor in this study was the insertion of the pump before skeletal maturity and therefore coinciding with the time when scoliosis may be developing naturally. A prospective study is recommended to gather further data on the development of scoliosis in this particular population with intrathecal baclofen pumps.
General comments	

Appendix 7

LIST OF EXCLUDED STUDIES

1. Zdolsek HA, Olesch C, Antolovich G et al. Intrathecal baclofen therapy. Benefits and complications. J Intellect DevDisabil. 2011;36(3):207-213
2. Haranhalli N, Anand D, Wisoff JH et al. Intrathecal baclofen therapy: complication avoidance and management. Childs Nerve Syst. 2011;27:421-427
3. van hilten BJ, van De Beek WT, Hoff JI et al. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Eng J Med. 2000;343:625-630
4. van der Plas AA, van Rijn MA, Marinus J et al. Efficacy of intrathecal baclofen on different pain qualities in complex regional pain syndrome. Anesth Analg. 2013;116:211-215
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8. Hoving MA, van Raak EPM, Spincemaille GHJJ et al. Intrathecal baclofen in children with spastic cerebral palsy; a double-blind, randomized, placebo-controlled, dose-finding study. Dev Med Child Neurol. 2007;49:654-659
9. Bonouvrie LA, van Schie PEM, Becher JG et al. Effects of intrathecal baclofen on daily care in children with secondary generalized dystonia: A pilot study. Eur J Paediatr Neurol. 2011;15:539-543
10. van der Plas AA, Marinus J, Eldabe S et al. The lack of efficacy of different infusion rates of intrathecal baclofen in complex regional pain syndrome: A randomized, double-blind, crossover study. Pain Med. 2011;12(3):459-465
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15. Dressnandt J, Conrad B. lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. J Neurol Neurosurg Psychiatry. 1996;60:168-173
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17. Plassat R, Perrourin Verbe B, Menei P et al. treatment of spasticity with intrathecal baclofen administration: long-term follow-up, review of 40 patients. Spinal Cord. 2004;42:686-693
18. Dvorak EM, McGuire JR, Melson MES. Incidence and identification of intrathecal baclofen catheter malfunction. PMR. 2010;2(8):751-756
19. Hester SM, Fisher JF, Lee MR et al. Evaluation of salvage techniques for infected baclofen pumps in pediatric patients with cerebral palsy. J Neurosurg Pediatr. 2012;10(6):548-554
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Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia,
Level 4, Block E1, Complex E, Precinct 1,
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 03 - 8883 1246/47
Fax: 03 - 8883 1230

ISBN 978-967-0769-11-0