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TECHNOLOGY REVIEW (MINI-HTA)

INTRAARTICULAR INJECTION OF HYALURONIC ACID COMBINED WITH SORBITOL / MANNITOL FOR OSTEOARTHRITIS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

Musculoskeletal conditions including osteoarthritis have been affecting the vast number of people worldwide and is the major contributor to years lived with disability. Osteoarthritis is a long-term chronic disease and is the most common musculoskeletal condition which involves in the thinning of joints cartilage contributing to pain, stiffness, impaired movement and reduced physical function. According to the analysis of Global Burden of Disease (GBD) periodic survey report in 2019, it is estimated that 1.71 billion people suffer from musculoskeletal conditions and about 343 million people suffer from osteoarthritis globally. The most affected countries are the high-income countries, subsequently the countries in the WHO Western Pacific Region and followed by South-East Asia Region.

According to the Malaysian Clinical Practice Guidelines (CPG) on Management of Osteoarthritis 2013, it is reported in the Community Orientated Program for the Control of Rheumatic Disease (COPCORD) study in Malaysia that 9.3% of Malaysian adults had knee pain with over half of them had clinical evidence of OA when examined. The prevalence ranged from 1.1% to 5.6% in the various ethnic groups and is likely to be underestimated. Malaysia is also coming to terms with increasing prevalence of OA due to its aging population and increasing prevalence of obesity.

Various pharmacological and non-pharmacological interventions are used to treat OA. Non-pharmacological interventions which are recommended for treatment of OA include patient education, lifestyle modification, physiotherapy, occupational therapy and orthoses. Pharmacological interventions utilised in the management of OA include a variety of oral treatment consists of simple analgesics, weak opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), Cyclo-oxygenase-2 Inhibitors and nutraceuticals. In patients with advanced age and multiple comorbidities, intra-articular injections have been increasingly favoured due to the potential side effects of NSAIDs.

Numerous intra-articular injections have been developed for the treatment of OA including corticosteroids, platelet-rich-plasma (PRP), and viscosupplementation with hyaluronic acid (HA) injection which is widely used in knee OA. The advancement of technology has resulted in the development of various formulations of hyaluronic acid in different molecular weights and origins or cross-linked hyaluronic acid. A newer version of intra-articular hyaluronic acid injection contains sorbitol or mannitol is claimed to prolong intraarticular hyaluronic acid residence time which may improve patient compliance and decrease complications as well as better analgesic action.

Hence, this technology review was conducted following the request from Medical Practice Division, Ministry of Health Malaysia to review the current best scientific evidence on intra-articular injection of hyaluronic acid combined with sorbitol or mannitol for osteoarthritis.

Objective/ aim

To assess the effectiveness, safety and cost-effectiveness of intra-articular injection of hyaluronic acid combined with sorbitol/mannitol for osteoarthritis.

Results and conclusion

From a total of 117 titles identified through the Ovid interface,15 studies were included in this review which were consisted of seven RCTs, one retrospective cohort study, six pre- and post- intervention studies, and one cross-sectional study. The included articles were published between 2012 and 2021. Most studies were conducted in France and Germany, followed by Spain, Turkey and Belgium.

Effectiveness

Intra-articular injection of Hyaluronic Acid combined with Sorbitol

There was very limited fair level of retrievable evidence to suggest that intra-articular injection of HA combined with sorbitol (IAHA + Sorbitol) was associated with pain reduction, improvement in stiffness and function with no significant difference compared to conventional IAHA in patients with knee OA.

Intra-articular injection of Hyaluronic Acid combined with Mannitol

There was limited fair level of retrievable evidence to suggest that intra-articular injection of HA combined with mannitol (IAHA + Mannitol) was associated with pain reduction, improvement in stiffness and function with no significant difference compared to conventional IAHA and placebo in one study, but clinically inferior to PRP in patients with knee OA. For hip OA and TMC OA, the evidence was insufficient to determine the effectiveness of IAHA + Mannitol in these populations.

Safety

There was no serious adverse event related to the intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis reported in the included studies.

Cost/Cost-effectiveness

There was no retrievable evidence on the cost-effectiveness of intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis.

Organisational

Guidelines

There was no guideline retrieved which specifically addressed the use of intra-articular injection of HA combined with sorbitol or mannitol in osteoarthritis. With regards to the use of intra-articular injection of HA in general, most guidelines found insufficient evidence to make a recommendation for or against the use of intra-articular HA for OA. Some guidelines recommend its use in certain situations, age groups and OA grade. The National Institute for Health and Care Excellence (NICE) and Osteoarthritis Research Society International (OARSI) recommended against the use of intra-articular injection of HA for knee OA. The American College of Rheumatology/Arthritis (ACR) Foundation strongly recommended against its use in patients with hip OA and conditionally recommended against its use in patients with knee and/or first carpometacarpal (CMC) joint OA.

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 March 2021), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2021), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2021), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020). 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 30th April 2021. Additional articles were identified from reviewing the references of retrieved articles.

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ABBREVIATION

AE	Adverse event
CASP	Critical Appraisal Skills Programme
CPG	Clinical Practice Guideline
COPCORD	Community Orientated Programme for Control of Rheumatic Disease
CI	Confidence Interval
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
GBD	Global Burden of Disease
HTA	Health Technology Assessment
HA	Hyaluronic acid
INAHTA	The International Network of Agencies for Health Technology Assessment
IAHA	Intra-articular injection of hyaluronic acid
IKDC	The International Knee Documentation Committee
KOOS	Knee Injury and Osteoarthritis Outcome Score
KSS	The Knee Society's Knee Scoring System
KSS	Newcastle-Ottawa Scale
NHMS	National Health Morbidity Survey
NSAID	Non-steroidal Anti Inflammatory Drug
NICE	The National Institute for Health and Care Excellence
OARSI	Osteoarthritis Research Society International
OA	Osteoarthritis
PASS	Patient Acceptable Symptom State
PGA	Patient Global Assessment
PRP	Platelet-rich plasma
RCT	Randomised controlled trial
RoB2	Cochrane Risk-of-Bias Tool for Randomised Trials
SR	Systematic review
THA	Total Hip Arthroplasty
TMC	Trapeziometacarpal
USFDA	United States Food and Drugs Administration
USA	United States of America
UK	United Kingdom
VAS	Visual Analog Score
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1.0 BACKGROUND

Musculoskeletal conditions including osteoarthritis have been affecting the vast number of people worldwide and is the major contributor to years lived with disability.[1] Osteoarthritis is a long-term chronic disease and is the most common musculoskeletal condition which involves in the thinning of joints cartilage contributing to pain, stiffness, impaired movement and reduced physical function.[2] Osteoarthritis is associated with various risk factors including modifiable and non-modifiable risk factors such as age, gender, genetic predisposition, bone density, obesity, lack of exercise, occupational injury, and trauma.[2]

According to the Global Burden of Disease (GBD) periodic survey report in 2019, it is estimated that 1.71 billion people suffer from musculoskeletal conditions and about 343 million people suffer from osteoarthritis globally.[3] The most affected countries are the high-income countries, subsequently the countries in the WHO Western Pacific Region and followed by South-East Asia Region.[2] In the United States of America (USA), osteoarthritis affects one in seven adults with approximately 32.5 million people in the country are diagnosed with osteoarthritis from 2008 to 2014 and more than half of these people are of working age.[4] Similarly in United Kingdom (UK), about one in 10 adults have osteoarthritis and both incidence as well as prevalence were found higher in women than men.[5]

According to the Malaysian Clinical Practice Guidelines (CPG) on Management of Osteoarthritis 2013, it is reported in the Community Orientated Program for the Control of Rheumatic Disease (COPCORD) study in Malaysia that 9.3% of Malaysian adults had knee pain with over half of them had clinical evidence of osteoarthritis when examined.[6] The prevalence ranged from 1.1% to 5.6% in the various ethnic groups and is likely to be underestimated.[6] Malaysia is also coming to terms with increasing prevalence of osteoarthritis due to its aging population and increasing prevalence of obesity. The percentage of the elderly aged ≥65 years has increased from 6.7% in 2019 to 7% in 2020, and these percentages are expected to reach 14.5% by 2040.[7] Likewise, the findings from the National Health Morbidity Survey (NHMS) 2019 showed an increase in the national prevalence of overweight, obese and abdominal obesity among adults which were 30.4%, 19.7% and 52.6% respectively compared to 30.0%, 17.7% and 48.6% respectively, in the previous study in 2015.[8] Various methods are used in OA classification including classification by the joint involved such as hand, hip and knee or by aetiologies.[6] The Kellgren-Lawrence grading system is the most widely used radiological classification for identification and grading of OA with radiographic grade 0 for no features of OA, grade I for doubtful, grade II for mild, grade III for moderate and grade IV for severe.[6]

Various pharmacological and non-pharmacological interventions are used to treat osteoarthritis. Non-pharmacological interventions which are recommended for treatment of osteoarthritis include patient education, lifestyle modification, physiotherapy, occupational therapy and orthoses.[6] Pharmacological interventions utilised in the management of osteoarthritis include a variety of oral treatment consists of simple analgesics, weak opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), Cyclo-oxygenase-2 Inhibitors and nutraceuticals.[6] In patients with advanced age and multiple comorbidities, intra-articular injections have been increasingly favoured due to the potential side effects of NSAIDs.[9]

Numerous intra-articular injections have been developed for the treatment of osteoarthritis including corticosteroids, platelet-rich-plasma (PRP), and viscosupplementation with hyaluronic acid (HA) injection which is widely used in knee osteoarthritis. The advancement of technology has resulted in the development of various formulations of hyaluronic acid in different molecular weights and origins or cross-linked hyaluronic acid. The intra-articular hyaluronic acid injection is generally given from three to five injections at weekly interval. A newer version of intra-articular hyaluronic acid injection contains sorbitol or mannitol is claimed to prolong intraarticular hyaluronic acid residence time which may improve patient compliance and decrease complications as well as better analgesic action.[10,11]

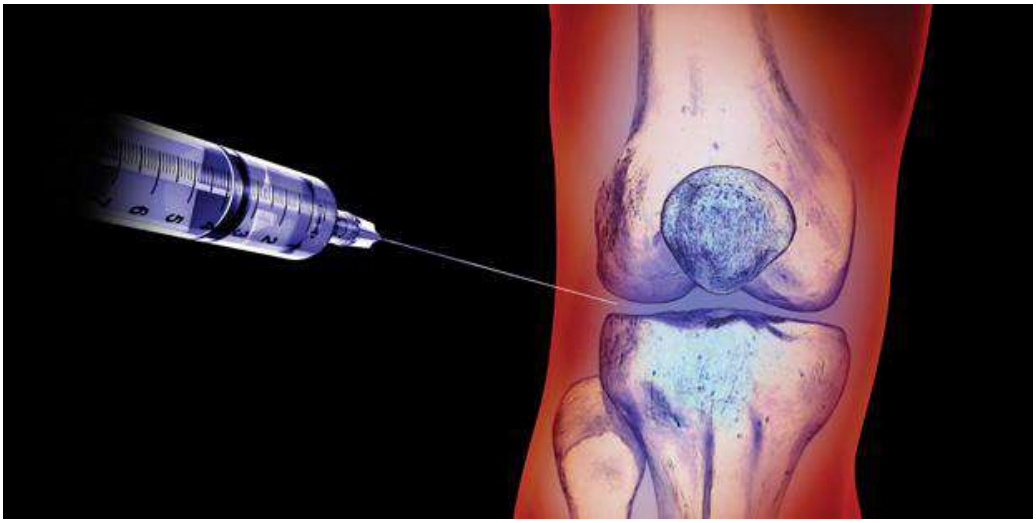
Hence, this technology review was conducted following the request from Medical Practice Division, Ministry of Health Malaysia to review the current best scientific evidence on intra-articular injection of hyaluronic acid combined with sorbitol or mannitol for osteoarthritis.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of intra-articular injection of hyaluronic acid combined with sorbitol/mannitol for osteoarthritis.

3.0 TECHNICAL FEATURES

Hyaluronic acid (HA) which is also known as hyaluronan, is a long, non-sulfated glycosaminoglycan that contains the repeating disaccharide unit of N-acetyl glucosamine and glucuronic acid.[12] It is responsible for the viscoelastic properties of the synovial fluid and cartilage extracellular matrix which act as shock absorber and joint lubricant.[13] Intra-articular injection of HA is most frequently used as a non-surgical therapy for osteoarthritis (OA). In patients with osteoarthritis, the concentration and molecular weight of endogenous hyaluronic acid in synovial fluid is diminished.[14] The intra-articular HA injection is claimed to improve chondrocyte HA and proteoglycan synthesis, as well as increases the production and activity of pro-inflammatory mediators and matrix metalloproteinases.[12] It is also thought to suppress cartilage degeneration and prevent cartilage for damage.[12] The intra-articular HA injection is claimed to be able to restore viscoelasticity through the replacement of dysfunctional synovial fluid and has analgesic effect because of modulation of early inflammatory response.[14]



There are a wide variety of formulations with different molecular weights for intra-articular HA produced by manufacturers worldwide. The recommended dosing regimens of intra-articular injection have generally ranged from three to five injections at weekly intervals. A more recent formulation combines sodium hyaluronate with a high concentration of the oxygen free radical scavenger mannitol or sorbitol. The addition of a scavenger and neutralizer of oxygen free radicals is claimed to delay the degradation of the injectable gel and may play a role in reducing the time to onset of analgesia consequently might allow for single injection regimen.[11,15]

Examples of intra-articular hyaluronic acid with mannitol/sorbitol available in the market worldwide: HAppyCross™ contains high concentration of hyaluronic acid (1.6%) 35.2 mg/syringe and high concentration of mannitol (77mg/syringe)[16], GO-ON Matrix contains 40mg of hyaluronic acid (2%) and 80mg sorbitol[17], Osteonil Plus contains hyaluronic acid (2%) and mannitol.[18]

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – March 2021
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2021

- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to March 2021
- EBM Reviews – Health Technology Assessment – 1st Quarter 2020
- EBM Reviews - NHS Economic Evaluation Database - 1st Quarter 2020

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on humans. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 30th April 2021.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with osteoarthritis
Interventions	Intra-articular hyaluronic acid with mannitol or sorbitol
Comparators	Other intra-articular hyaluronic acid injection Other intra-articular injections No comparator
Outcomes	Effectiveness: Pain reduction, morbidity, mortality Adverse effects, complications, safety issues, Cost-effectiveness, cost-utility, cost-minimisation, cost-analysis and economic evaluation Organisational –guidelines, recommendations
Study design	Health Technology Assessment (HTA), Systematic reviews (SR), Randomised control trials (RCTs), observational studies
Type of publication	English, full text articles

Exclusion criteria

Study design	Case report, survey, anecdotal, animal studies
Type of publication	Non-English
Intervention	Intra-articular hyaluronic acid without mannitol or sorbitol

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed

data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 117 titles were identified 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 March 2021), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2021), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2021), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020) and PubMed. The last search was run on 30th April 2021. Additional articles were identified from reviewing the references of retrieved articles.

Twenty-five articles were identified from references of retrieved articles. After removal of 15 duplicates, 127 titles were screened. A total of 127 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 92 abstracts were found to be irrelevant. Thirty-five potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 35 full text articles, 15 full text articles were included and 20 full text articles were excluded. (Figure 1). The review included 15 studies which were consisted of seven RCTs, one retrospective cohort study, six pre- and post- intervention studies, one cross-sectional study.

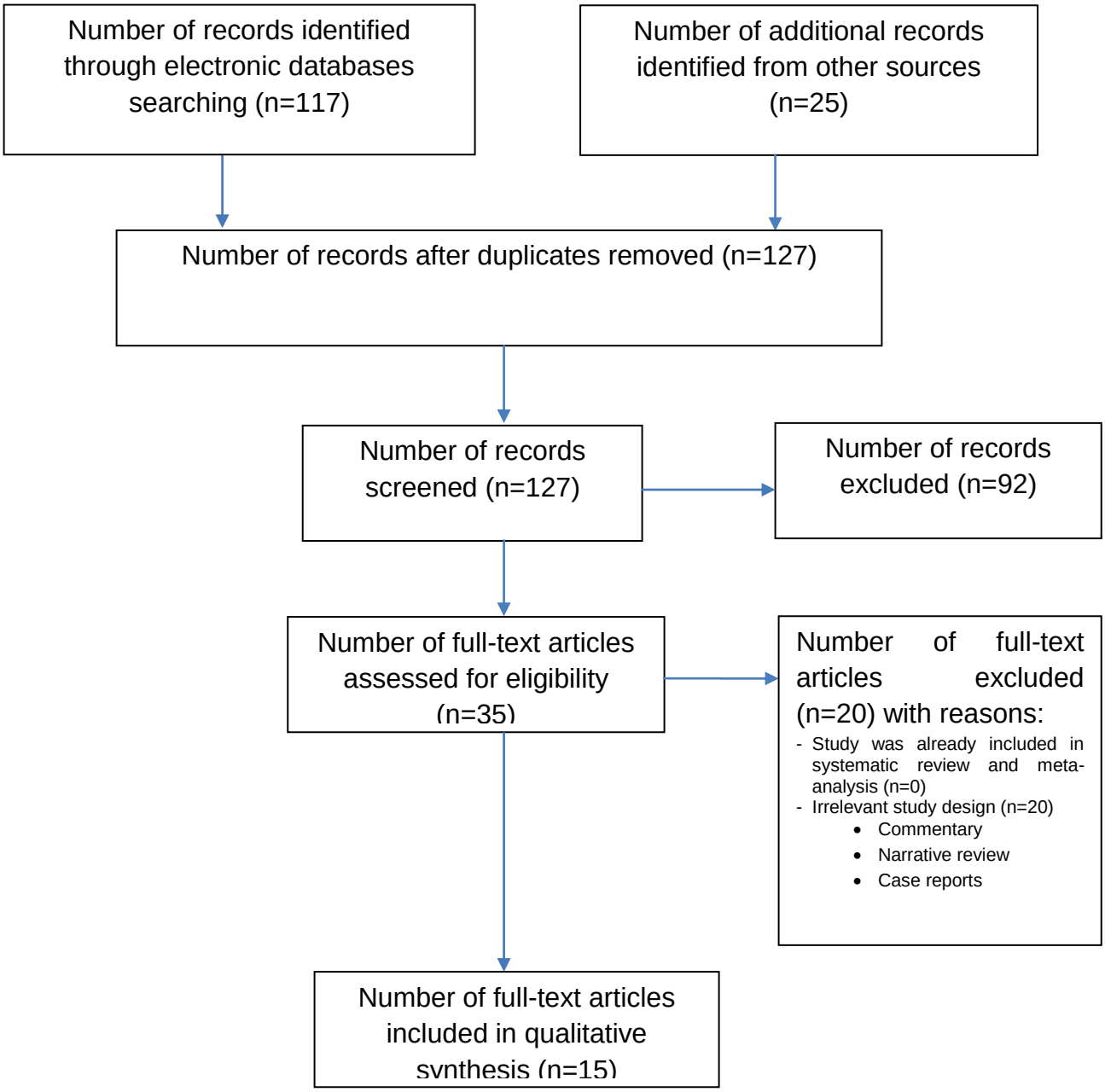


Figure 1: Flow chart of study selection

The included articles were published between 2012 and 2021. Most studies were conducted in France and Germany, followed by Spain, Turkey and Belgium.

5.1 RISK OF BIAS / QUALITY ASSESSMENT OF INCLUDED STUDIES

The methodological quality of all the relevant full text articles retrieved was assessed using the relevant checklist of Cochrane Collaboration Assessment tools, Critical Appraisal Skills Programme (CASP) and NIH Quality Assessment Tool depending on the type of the study design. It is done by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates low risk of bias
?	indicates unclear risk of bias / some concerns
-	Indicates high risk of bias

Assessment of Randomised Controlled Trial (RCT) using Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2)

The risk of bias of RCTs included in this review was assessed using Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2)[19] checklist. Seven RCTs[20-25,33] were included in this assessment. The risk of bias is shown in Figure 2. There was no information on allocation concealment in the RCTs by Barac B et al. (2019)[22] and Duymus T et al. (2017)[23] thus was judged as 'some concerns' for that domain and overall. The other five RCTs were judged to have low risk of bias in all domains assessed.

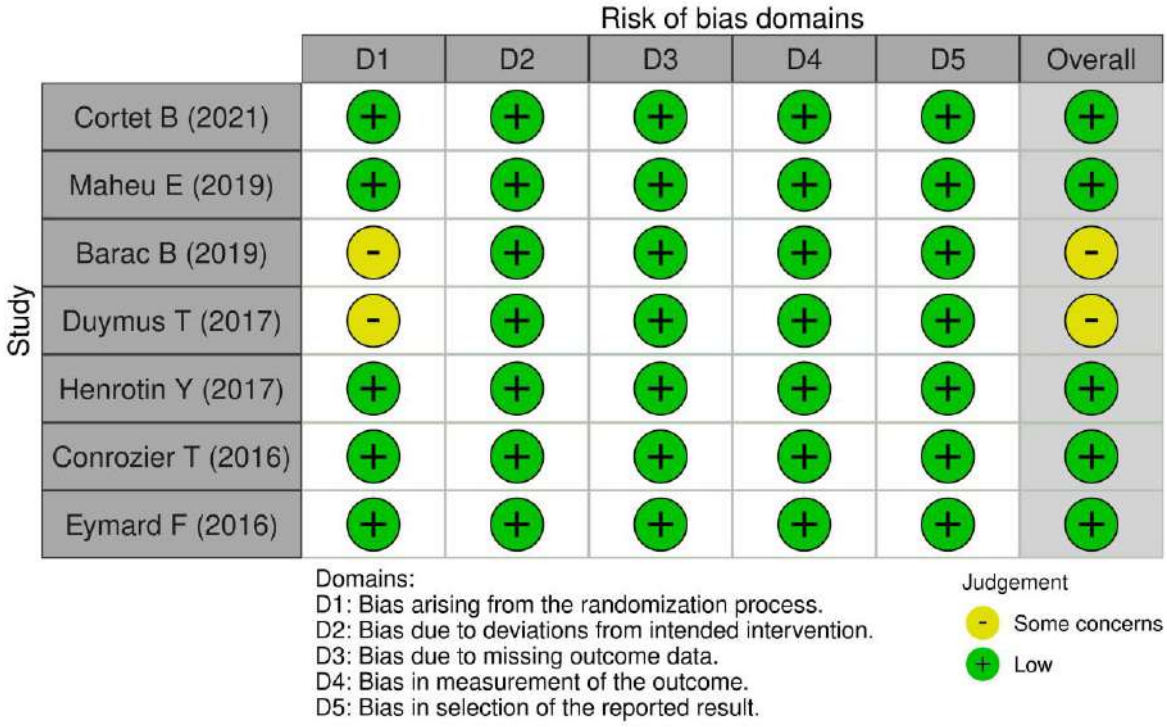


Figure 2: Assessment of risk of bias of RCT (RoB2)

Assessment of Cohort Study using Critical Appraisal Skills Programme (CASP) Checklist

Figure 3 shows the risk of bias of one retrospective cohort study by Guler O et al. (2015)[26] based on the CASP checklist. The study was at low risk of bias for all five domains assessed.

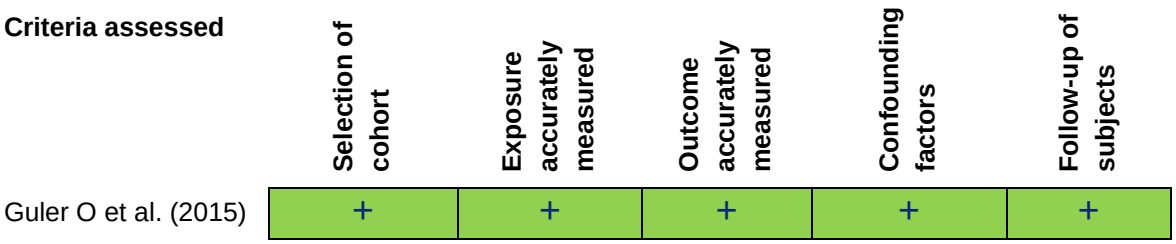


Figure 3: Quality assessment of cohort studies (CASP)

Assessment Using NIH Quality Assessment Tool For Before-After (Pre-Post) Studies With No Control Group

The risk of bias for Pre-Post studies with no control group was assessed using NIH Quality Assessment Tool. Six studies[27-32] were included in this assessment. Figure 4. shows the summary of the risk of bias for these studies. All of the studies did not describe specifically whether the investigators were blinded to the patients' intervention. Dauvissat J et al. (2018)[27] and Monet M et al. (2017)[28] did not use interrupted time series design. Three studies which were Monet M et al. (2017)[28], Conrozier T et al. (2016)[29] and Borras-Verdera A et al. (2012)[32] had small sample size of 53, 40 and 80 patients with knee OA respectively. Heisel J et al. (2013)[30] had one high risk criteria which were loss to follow-up of more than 20% after baseline.

Criteria assessed	Dauvissat J et al. (2018)[27]	Monet M et al. (2017)[28]	Conrozier T et al. (2016)[29]	Heisel J et al. (2013)[30]	Heisel J et al. (2012)[31]	Borras-Verdera A et al. (2012)[32]
Question or objective clearly stated?	+	+	+	+	+	+
Eligibility/selection criteria for study population clearly described?	+	+	+	+	+	+
Were participants representative for those who would be eligible for the test/ service/intervention in the population of interest?	+	+	+	+	+	+
Were all eligible participants that met the pre-specified entry criteria enrolled?	+	+	+	+	+	+
Sample size sufficiently large to provide confidence in findings?	+	?	?	+	+	?
Test/service/intervention clearly described and delivered consistently?	+	+	+	+	+	+

Outcome measures pre-specified, valid, reliable, and assessed consistently?	+	+	+	+	+	+
People assessing the outcome measures blinded to participants exposure/ interventions?	?	?	?	?	?	?
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	+	+	+	-	+	+
Statistical methods examine changes in outcome measures from before to after intervention? P value?	+	+	+	+	+	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	-	-	+	+	+	+
If intervention conducted at group Level, did statistical analysis consider of individual Level data to determine effects at group Level?	+	+	+	+	+	+

Figure 4: Assessment of risk of bias of (Pre-Post) Studies with No Control Group

5.2 EFFECTIVENESS

There were 15 studies retrieved on the effectiveness of intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis. Of the 15 studies, one RCT and two pre- and post- intervention studies were related to the effectiveness of intra-articular injection of HA combined with sorbitol while the other five RCTS, one retrospective cohort study, four pre- and post- intervention studies, one cross-sectional study and one retrospective analysis of an included RCT were related to the effectiveness of intra-articular injection of HA combined with mannitol.

5.2.1 Intra-articular injection of Hyaluronic Acid combined with Sorbitol

Cortet B et al. (2021) conducted an RCT in France to determine the non-inferiority of an intra-articular injection of HA combined with sorbitol 4% (IAHA + Sorbitol) with another intra-articular injection of HA (IAHA) in patients with knee OA (Kellgren and Lawrence radiological stage II or III) in whom oral treatment was insufficient or poorly tolerated. A total of 202 patients were enrolled in the study and randomised to one of the two treatment groups (IAHA + Sorbitol, n= 96, or IAHA, n= 106). On Day 0, the physician administered viscosupplementation. The patients were then followed-up from Day 1, Day 7, Day 28, Day 84 till Day 168. Symptoms of OA including pain, functionality and stiffness were evaluated. The primary efficacy variable was the comparison between the two injections regarding the change between Day 168 and Day 0 of the overall Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score. Secondary outcomes of interest included the evolution of pain at Day 7, WOMAC pain, stiffness and total scores at Day 28, Day 84 and Day 168. The safety of each product was monitored, and adverse events (AE) were recorded. The patients included were predominantly female (66%) with median age of 65 years, and the median body mass index was 27.4 kg/m2. Over half of the patients (70%) had a Kellgren-Lawrence OA grade of III. No statistically significant difference between the two treatment groups was observed for any demographic criteria. The study found that the WOMAC pain score decreased in the two groups: − 29.2 ± 24.1 (SD) in the IAHA +Sorbitol group and − 31.6 ± 25.5 (SD) in the IAHA group, p = 0.57, showing the non-inferiority of intra-articular injection of HA combined with sorbitol. Regarding the secondary end points, significant decrease in pain was seen at day seven and

continued throughout the study with no significant difference between the groups. There was significant score improvement in stiffness and function as well as in the total score of WOMAC from baseline to Day 168 with no significant difference between the groups. No statistically significant difference was observed in neither patient-assessed global pain satisfaction at Day 168 nor in the investigator assessment of treatment efficacy using Likert scale at Day 168 for both groups.[20 Level II-1]

Heisel J et al. (2013) conducted a pre- and post- intervention study in Germany to assess safety and efficacy of the intra-articular injection of HA combined with sorbitol in OA. A total of 1,147 patients with OA were enrolled and patients were interviewed on Day One for screening and data collection on diagnosis, medical history, and medications. Knee was the most commonly treated joint (92.9 %) with a Kellgren-Lawrence classification of Grade I (6.7 %), Grade II (31.4 %), Grade III (48.0 %), and Grade IV (13.9 %). Patients' pain and functional impairment due to OA were assessed before the first injection on Day One and at weeks four, 12 and 24. Possible adverse reactions were recorded. Patient subjective assessments of pain and functional impairment due to OA were performed prior to injection using Likert scale from none (0), mild (1), moderate (2), severe (3), to very severe (4). Global subjective assessments of the OA treatment efficacy were performed independently by both the patient and the investigator using a five-point scale from much better, through better, no change, worse, to much worse. The study showed that majority of patients received one intra-articular injection of HA combined with sorbitol while 29-40% received three injections. With regards to pain, there was reduction of 56.5% from baseline to six months. The proportion of patients with severe or very severe pain due to OA reduced markedly from 56.2 % at baseline to 6.2 % after three months and 5.9 % six months after the first injection. Similarly, the proportion of patients with no pain, or only mild pain increased from 6.8 % at baseline to 66.8 % after three months, and 67.1 % six months after the first injection. In terms of functional impairment, the percentage of patients with severe or very severe functional impairment due to OA reduced from 29.1 % at baseline to 3.6 % after three months, and 3.9 % six months after the first injection. The percentage of patients with mild or no impairment improved from 28.9 % at baseline to 66.4 % after both three months and six months post injection. Investigator rated the treatment success as better than conventional HA therapies for 48.9 % of patients and equivalent for 33.9 % at the final assessment.[30 Level II-3]

Another pre- and post- intervention study has been conducted by Heisel J et al. (2012) in Germany involving 101 patients with long-standing knee OA to examine the efficacy and tolerability of intra-articular HA combined with sorbitol. The included patients received three intra-articular injections of HA combined with sorbitol (IAHA + Sorbitol) into the affected knee joint at intervals of one week. Patients' pain symptoms were recorded at the start of study till 24 weeks after the first injection. The results showed that only 4% of patients have no pain at the start of treatment while 21.8% of patients suffered severe or very severe pain. After each of the three injections of IAHA + Sorbitol, the percentage of patients who are pain-free increased steadily from 16.8% after the first injection to 40.6% after 24 weeks. Concurrently, the proportion of patients with moderate, severe or very severe pain reduced substantially during treatment from 21.8% to 5% after the first injection. About 74.3% of the patients reported pain reduction at 24 weeks after the start of treatment. In addition, there was reduction in the extent of functional impairment with 14.9% of patients complained of severe or

very severe impairment before treatment, but only 4% complained of this degree of impairment after the first injection. The proportion of patients with no functional deficit increased from 31.7% to 51.5%. The proportion of patients who reported improvement increased from 64.4% one week after the first injection to 87.1% a week after the third injection, while assessment by the doctors improved from 57.4% to 82.2%.[31 Level II-3]

5.2.2 Intra-articular Injection of Hyaluronic Acid combined with Mannitol

Knee Osteoarthritis

Maheu E et al. (2019) conducted an RCT in France involving 292 patients from 50 centres to determine the non-inferiority of a single intra-articular injection of HA combined with mannitol (IAHA + Mannitol) compared to conventional intra-articular injection of HA (IAHA) in symptomatic knee OA. Patients were randomised into two groups; 144 patients in the IAHA + Mannitol group and 148 patients in the IAHA group. The primary outcome of interest was the change from baseline to six months after injection in the WOMAC pain subscale (WOMAC A). Stiffness (WOMAC B) and function (WOMAC C) subscales of the WOMAC were assessed as secondary outcomes of interest. The patients included in the study were mostly women (66.4%), moderately overweight and the mean age was 66.9 ± 10.2 years (39–86 years old). Approximately 56.5% of the included patients had a grade II modified Kellgren-Lawrence knee OA. Symptoms were moderate to severe, with mean WOMAC subscores of the studied knee for pain (58.3 ± 11.7 mm), stiffness (48.3 ± 20.3 mm) and function (47.7 ± 15.8 mm). From 292 randomly assigned patients, 142 patients received a single injection of IAHA + Mannitol, another 146 patients received conventional IAHA and four patients did not. There were 22 patients (eight patients in IAHA + Mannitol group and 14 patients in IAHA group) who discontinued the study prematurely [(IAHA + Mannitol group; consent withdrawal (n=5), lack of efficacy (n=1), forbidden treatment (n=1), adverse events (n=1), IAHA group; consent withdrawal (n=4), lack of efficacy (n=1), forbidden treatment (n=4), adverse events (n=4), other (n=1)] and two patients in each group were lost to follow-up. The results showed that the WOMAC A change at six months was -34.3 mm (95% confidence interval (CI): -37.8, -30.8) for IAHA + Mannitol patients and -36.2 mm (95% CI: -40.3, -32.1) for conventional IAHA patients (P = 0.5) demonstrating the non-inferiority. The intergroup difference was -2.9 mm (95% CI: -7.9, 2.2). Significant improvements in stiffness and function were noted in both groups after treatment (P <0.001), which was maintained up to the end of the study. [21 Level II-1]

A randomised controlled trial was carried out by Barac B et al. (2019) in Belgrade, Serbia to compare the efficacy of intra-articular injections of platelet rich plasma combined with HA (PRP+HA group) versus intra-articular injection of HA (IAHA group) and HA combined with mannitol (IAHA+ mannitol group) for the treatment of knee OA. Fifty-three (90 knees) patients with knee OA were allocated into three groups; 19 patients (30 knees) were treated with three intra-articular injections of PRP combined with HA (PRP + HA) in two weeks interval, 19 patients (30 knees) were treated with three weekly intra-articular injections of HA (IAHA) and 15 patients (30 knees) were treated with three weekly intra-articular injections of HA combined with mannitol (IAHA + Mannitol). Visual analog pain scale (VAS), WOMAC, Knee Injury and Osteoarthritis Outcome Score (KOOS), The International Knee Documentation Committee (IKDC) score and ultrasound cartilage thickness on lateral, trochlear, and medial

compartments were measured at baseline and at two, six and 12 months after the last injection. The study found that there were statistically significant differences in PRP + HA group compared to IAHA group and IAHA + Mannitol group in VAS, WOMAC, KOOS and IKDC scores at two months ($p<0.05$), six months ($p<0.01$) and 12 months ($p<0.01$) after the last injection. Deterioration in VAS, WOMAC, KOOS and IKDC scores were noted in both IAHA group and IAHA + Mannitol group after 12 months compared to six months post injections.[22 Level II-2]

Henrotin Y et al. (2017) conducted an RCT in Belgium to assess the effect of an intra-articular injection of HA combined with mannitol (IAHA + Mannitol) versus saline injection on the level of a specific biomarker of type II collagen degradation as well as on pain symptoms and function in 81 patients with symptomatic knee OA. Eighty-one patients were randomised into two groups: 40 in the IAHA + Mannitol group and 41 in the saline solution group. Four patients finished prematurely the study: one (2.5%) from the treatment group due to AE, 3 (7.3%) from the saline solution group (one for AE, one for AE and inefficacy, one for loss of follow up). Primary outcome of interest was the percentage of patients with a reduction of at least 10 nmol/l of serum Coll2-1 between baseline and three months post injection. Secondary outcomes included clinical evaluation on pain, function and tolerance to the injection. The study found that there was no statistically significant difference in the percentage of patient with a reduction of at least 10 nmol/l of serum Coll2-1 between day 10 and day 90 (52.5% in the treatment group and 31.7% in the saline group, $p=0.05$). There was no significant change in pain (VAS) and function from baseline till day 90 post injection. There was also no statistically significant difference between groups regarding the change in function or pain (VAS) as well as consumption of analgesics.[24 Level II-2]

Duymus T et al. (2016) conducted an RCT in Istanbul, Turkey to to compare the efficacy of three treatments for patients with knee OA; intra-articular injection of platelet-rich plasma (PRP), intra-articular injection of HA combined with mannitol (IAHA + Mannitol) and intra-articular injection of ozone gas. A total of 120 patients were randomised into three groups: 41 patients in PRP group, 40 patients in IAHA + mannitol group and 39 patients in the ozone group. The PRP group received two doses of PRP, the IAHA + mannitol group received a single dose of injection and ozone group received four doses of gas injections. Both knees were evaluated for weight-bearing anteroposterior-lateral and Merchant's radiographs. Primary outcome of interest was the change in WOMAC and VAS scores from the first presentation and at one, three, six and 12 months. The study found significant improvements in all groups at the end of first month post injection compared to baseline ($p < 0.001$). At three months post injection, improvements in WOMAC and VAS scores were noted similar in PRP group and IAHA + Mannitol group, whereas lower scores were noted in ozone group ($p<0.001$). At six months, while the clinical efficacies of PRP and IAHA + Mannitol were similar and continued, the WOMAC and VAS scores of the Ozone group had completely returned to baseline values and the clinical effect had disappeared ($p < 0.001$). At 12 months post injection, in the PRP group, the VAS score decreased to a mean of 29 ± 0.27 %, while in IAHA + Mannitol group, the VAS score decreased to a mean of 18 ± 0.13 % compared to baseline. The total WOMAC score decreased to a mean of 27 ± 0.16 % in the PRP group, while in the IAHA + Mannitol group, the total WOMAC score decreased to a mean of 10 ± 0.07 %. There was statistically significant

difference between PRP group and IAHA + Mannitol group with PRP was clinically superior to IAHA + Mannitol group (p<0.001).[23 Level II-2]

Another study conducted by Conrozier T et al. (2016) was an RCT done in France. The study aimed to determine the non-inferiority of a novel intra-articular hyaluronic acid (HA) mixed with high concentration of mannitol (IAHA + Mannitol) with IAHA in patients with knee OA. A total of 222 patients were randomised into two groups; 109 patients in the treatment group (IAHA + Mannitol) while 113 patients in the control group (conventional IAHA). Both injections were supplied in similar syringes containing two milliliters of HA solution and were administered, one week apart, three consecutive weeks, into the target knee by an orthopaedic surgeon or rheumatologist. The primary outcome of interest was the change in WOMAC pain subscale at six months post injection. Secondary outcomes of interest were the six-month change in function and walking pain, analgesic consumption as well as safety issues. The study showed that the mean (SD) variations in WOMAC pain score were −4.4 (3.8) and −4.5 (4.3) mm, for IAHA + Mannitol and IAHA respectively, demonstrating non-inferiority. Similar results were obtained for all other secondary outcomes of interest. The average six-month change in the walking pain was −2.9 (2.8) for IAHA + Mannitol and −2.6 (2.4) for IAHA (p=0.49). About 82.6% of patients considered there were symptoms improvements at three months and 85.5% considered there were symptoms improvements regardless the treatment groups. In terms of analgesic consumptions, about 58.2% of patients had reduction in analgesic intake between six months with 49.2% in the IAHA + Mannitol group compared to 56.3% in the conventional IAHA group with no significant difference between groups (p=0.73). Both groups showed similar percentages of patients who completely stopped analgesics intake with about 23.8% of patients in IAHA + Mannitol group compared to 28.8% in conventional IAHA group (p=0.72).[25 Level II-1] Eymard F et al. (2016) used data from this RCT to compare the speed of action of three weekly IAHA + Mannitol with conventional IAHA in patients with knee OA. The primary outcome was the change in WOMAC pain subscale at week one and week two. Percentages of patients with improvements as well as level of improvement were also recorded. The analysis showed that the median (range) of the WOMAC pain sub-score was 9.0 (4-19), 6.0 (0-19) and 5.0 (0-15) in the IAHA + Mannitol at baseline, week two and week three post injection respectively, compared to 9.0 (2-18), 7.0 (0-16) and 6.0 (0-14) in the conventional IAHA group showing a decrease in pain score in the treatment group however the difference was not statistically significant. The average decrease of pain (SD) was found greater in the IAHA + Mannitol group compared to the conventional IAHA group at both week two: -3.0 (3.6) versus -1.9 (3.1) respectively, p=0.10 and at week three: -4.2 (3.2) versus -2.8 (2.6) respectively, (p=0.048) in patients with more severe joint space narrowing.[33 Level II-1]

Guler O et al. (2015) conducted a retrospective cohort study to compare short-term clinical outcomes between intraarticular PRP and HA treatments in early-stage knee OA patients. Data of patients with knee OA who were in stage I or stage II according to Kellgren–Lawrence classification and underwent intraarticular PRP or HA treatment in an Orthopaedic Clinic in Turkey between February 2011 and November 2012, were retrospectively reviewed. A total of 63 patients (86 knees) received intra-articular injection of HA combined with mannitol (IAHA + Mannitol) and 69 patients (89 knees) received PRP. All patients received treatment three times weekly. The Knee Society's Knee Scoring System (KSS) was used for clinical and functional evaluation and VAS

scoring system was used for pain evaluation before treatment and at two months as well as at six months post treatment. Demographic characteristics of the patients, complications and adverse events during treatment were recorded. The results showed that no significant difference was noted between the treatment groups in terms of gender, age, body mass index (BMI), distribution among stages, and unilateral/bilateral involvement. There was significant increase in the KSS score from baseline to two months after treatment ($p<0.001$) which was noted higher in the PRP group (difference between the scores in the PRP group: 17.61 ± 5.61) compared to the IAHA + Mannitol group (difference between the scores: 10.01 ± 0.11, $p<0.001$). Similarly, there was significant increase in the KSS score from second month to post-treatment sixth month ($p<0.001$) which was noted higher in the PRP group (difference between the scores: 10.85 ± 5.17; $p = 0.008$) compared to the IAHA + Mannitol group (difference between the scores: 8.78 ± 3.28; $p = 0.008$). In terms of VAS scores, pre-treatment and post-treatment second month and sixth month were significantly lower in the PRP group than in the IAHA + Mannitol group. The decrease was greater in the PRP group (difference between the scores: -3.01 ± 1.01 than in the HA group (difference between the scores: - 1.83 ± 0.56; $p<0.001$). Decrease in VAS score from post-treatment second month to post-treatment sixth month was significant ($p<0.001$) but there was no significant difference between groups (difference between the scores in the PRP group: -1.10 ± 1.07 versus difference between the scores in the IAHA + Mannitol group: - 1.07 ± 0.61, $p=0.161$).[26 Level II-2]

A pre- and post- intervention study was conducted by Monet M et al. (2017) to assess safety and efficacy of a single intra-articular injection of a cross-linked HA combined with mannitol involving 53 symptomatic knee OA patients in France. Patients' data were taken from a cohort of patients referred to the department of rheumatology of the North Franche-Comté hospital in Belfort, France between February and August 2016 who were treated with a single intra-articular injection of HA combined with mannitol. Primary outcome of interest was the six months changes in the WOMAC pain, function and total and the patient's global assessment (PGA). Patient Acceptable Symptom State (PASS) and Minimum Clinically Important Improvement (MCII) were calculated from WOMAC pain sub-score. Patient's self-assessment of treatment efficacy and analgesic consumption were also recorded. All adverse events were monitored. The study found that compared to baseline values, the mean decrease of WOMAC score after six-month post-injection was more than 50% for both pain and function ($P<0.0001$). At month 6, 82% of patients were PASS + and 86.8% had experienced improvement > MCII threshold.[28 Level II-3]

Conrozier T et al. (2016) conducted a pre- and post- intervention study in France to determine safety and efficacy of an intra-articular injection of cross-linked sodium hyaluronate concentrated at 16 mg/mL combined with a high concentration (3.5%) of mannitol, administered through a single injection in patients with symptomatic knee OA. Data of 40 consecutive patients who were followed up for six months after receiving the intra-articular injection of HA combined with mannitol (IAHA + Mannitol) were retrospectively gathered. The primary outcome was safety. The secondary outcomes included three- and six-month change in the WOMAC pain (0–50) and WOMAC total (0–240) as well as patient's global assessment (PGA). Patient's self-assessment of treatment efficacy and analgesic consumption were recorded at three- and six-months post injection. The study found that at baseline, the average WOMAC

pain and WOMAC total scores were 21.5 (9.8) and 89.9 (42.8), respectively. At six months, the mean (SD) variations in WOMAC pain and WOMAC total scores were −8.2 (8.9) and −38.4 (35.6), respectively (*P* = 0.001). Patient Global Assessment (PGA) decreased from 5.5 (2.0) to 3.0 (2.2) (*P* = 0.006). Efficacy was rated as *good or very good* in 76.9% of the cases and reduction in the use of analgesics were noted in most of the regular analgesics users.[29 Level II-3]

A pre- and post- intervention study has been done by Borrás-Verdera A et al. (2012) in Spain involving 80 patients to examine safety and efficacy of a single intra-articular injection of 2% hyaluronic acid (HA) combined with mannitol in symptomatic knee OA. The included patients received an intraarticular injection of HA combined with mannitol at their first visit and were then followed-up for six months. Pain and joint function were assessed using VAS and WOMAC index on Days 0, 15, 30, 60, 90, 120, 150 and 180. Physician and patient's opinion regarding treatment efficacy and tolerance were recorded as well as adverse events. The results showed that there was statistically significant reduction in joint pain, stiffness and functional disability compared at baseline at every follow-up visit (*P* < 0.001). There was improvement in joint function by 38.7% at Day 30 and increased to 47.5% at Day 180. The use of rescue medication had decreased from 58.2% at baseline to 2.5% at Day 90 and increased again in the last visits. The mean assessment of effectiveness by the investigator and patient (scored from worst to ideal) was good or very good throughout the study. Statistically significant differences in efficacy score between first assessment and subsequent visits were noted except in the last visit which suggested that symptoms had started to reappear after six months of treatment.[32 Level II-3]

Hip Osteoarthritis

Conrozier T et al. (2014) conducted a cross-sectional study in France to assess patients' self-evaluation of efficacy, satisfaction and tolerability of a single intra-articular injection of HA combined with mannitol (IAHA + Mannitol) in patients with symptomatic hip OA and to examine if viscosupplementation with this injection could be an alternative to hip replacement in patients who refused surgery or in waiting list for surgery. A total of 191 patients who received the IAHA + Mannitol within six months were interviewed by phone using standardised questionnaire. Data on demographic, analgesic intake, imaging guidance during injection, pain assessment using 10-point Likert scale, patients' self-evaluation of efficacy, satisfaction and tolerability were taken. Patients were divided into two groups; the total hip arthroplasty (THA) group (n=123) consisted of patients for whom viscosupplementation with intra-articular injection of HA combined with mannitol was the last option before surgery, and the no-surgery group (n=68) consisted of patients who would not consider surgery. The results showed that patients in the THA group were mainly man and NSAIDs users however were not significantly different with regards to age compared to the no-surgery group. The percentage of patients who were very satisfied with the intra-articular injection was 24.6%, satisfied was 27.7%, not really satisfied was 22.5% and not satisfied at all was 25.1%. The efficacy was considered as very good/good in 86.4%, moderate in 23.6%, and poor in 24.6% of patients. Efficacy was highly correlated to pain (p<0.0001) and was unrelated to age, gender and imaging guidance. In satisfied patients, the decrease of analgesics or NSAIDs intake was >75% in 60.5% of cases. The results showed that about 66.6% patients in the no-surgery group were

satisfied with the intra-articular injection of HA combined with mannitol compared to only 25% in the THA group (p<0.0001).[34 Level III]

Trapeziometacarpal (TMC) Osteoarthritis

Dauvissat J et al. (2018) conducted a pre- and post- intervention study in France to assess the patient perception of pain and treatment efficacy of an intra-articular injection of HA combined with mannitol (IAHA + Mannitol) in patients who suffer trapeziometacarpal (TMC) OA. About 122 patients with symptomatic TMC OA which was not sufficiently relieved by first-line treatments were included in the study. All patients received IAHA + Mannitol under ultrasound or radiological guidance. Data on patient self-assessment of pain measured on an 11-point numerical rating scale (0-10NS), and radiological features (Dell stage 1-4) were taken at baseline. After three months post injection, data on patient self-assessment of pain, patient perception of treatment efficacy using a 4-point NS (0 meaning not effective, 1 slightly effective, 2 effective, and 3 very effective), variation in analgesic intake (in percentage comparing with the consumption before the injection), and the occurrence of any adverse event (AE) were recorded. The primary outcome of interest was the variation in the pain scores between the injection day and three months after. The secondary outcomes of interest included the patient perception of treatment efficacy and the variation in the use of painkillers. The study reported that most included patients were women, the average age was 60 years, and the average disease duration was 36 months. The TMC OA was of Dell's grade 1, 2, 3, and 4 in 23%, 36.8%, 36.8%, and 3.5% of cases, respectively. At injection day, the average (SD) pain level was 6.5 ± 1.6 and decreased to 3.9 ± 2.5 (difference −2.7 ± 2.5; −42%; $P < .0001$) at Day 90. About 69% of patients estimated the treatment as effective (21% very effective, 31% effective, 17% slightly effective) and 21% rated it ineffective. In 78% of cases, analgesic consumption decreased by more than 50% and in 66% of cases by more than 75%.[27 level II-3]

5.3 SAFETY

There were one RCT and one pre- and post- intervention study retrieved on safety of intra-articular injection of HA combined with sorbitol for osteoarthritis. Meanwhile, there were four RCTs, one retrospective cohort study, four pre- and post- intervention studies and one cross-sectional study retrieved on the safety of intra-articular injection of HA combined with mannitol for osteoarthritis.

5.3.1 Intra-articular injection of Hyaluronic acid with Sorbitol

Cortet B et al. (2021) reported in their RCT that the intra-articular injection of HA combined with sorbitol had comparable safety profile with the conventional intra-articular injection of HA. The injection was well tolerated in patients. Eighty-six patients reported AEs during the study, 46 AEs in the IAHA + Sorbitol group and 40 AEs in the IAHA group. Forty-six of those were related to the treatment with 37 related to underlying musculoskeletal disorders and 9 related to injection site abnormalities. There was no statistically significant difference between the groups.[20 Level II-1]

In the pre- and post- intervention study by Heisel J et al. (2019), it was reported that most patients tolerated the intra-articular injection of HA combined with sorbitol well.[30 Level II-3] The most reported AE was injection site joint pain (n = 15).[30 Level II-3] It was noted that reactions to the injections were more common after the first injection which were mostly pain in joint.[30 Level II-3] Swelling and effusion also occurred in about 1.2% and 1.0% of patients respectively, after the first injection.[30 Level II-3] No joints infections were reported.[30 Level II-3] In another earlier pre- and post- intervention study by Heisel J et al. (2012), there were no local or systemic adverse effects related to the intra-articular injection of HA combined with sorbitol were reported.[31 Level II-3]

5.3.2 Intra-articular injection of Hyaluronic acid with Mannitol

Maheu E et al. (2019) reported in their RCT that patients tolerated the intra-articular injection of HA with mannitol well, and the proportions of patients reporting AE were similar between the intra-articular injection of HA with mannitol (27.5%) and the conventional intra-articular injection of HA (34.9%). A total of 31.3% of the injected patients reported AE with injection site reactions (pain, inflammation or effusion) being the most common AE which occurred in 8.5% of the IAHA + Mannitol patients compared to 13.0% of the IAHA patients. No serious reactions were reported, and all patients recovered from their AEs.[21 Level II-1]

In the RCT by Barac B et al. (2019), it was reported that only three patients in the intra-articular injection of HA with mannitol experienced mild inflammatory reactions which lasted for a maximum of 12 hours. [22 Level II-2] Dauvissat J et al. (2018) reported that 11% of patients in their pre- and post- intervention study experienced transient increase in pain during and following administration of intra-articular injection of HA combined with mannitol which resolved spontaneously within one to seven days. [27 level II-3] A pre- and post- intervention study was conducted by Monet M et al. (2017) and reported three patients (5.7%) had transient worsening of pain following the intra-articular injection of HA combined with mannitol which resolved spontaneously within 36 and 72 hours. [28 Level II-3] No systemic AE and severe AE related to the injection was reported. [28 Level II-3]

Henrotin Y et al. (2017) reported in their RCT that there were 30 adverse events reported in 29 patients (35.8%) with 14 in the intra-articular injection of HA combined with mannitol group and 15 in the saline group. Two AEs were considered attributable to the product, one joint effusion in the treatment group and one inflammation at the injection site in the saline solution group. No serious AEs related to the treatment was reported. [24 Level II-2]

Conrozier T et al. (2016) described in their pre- and post- intervention study that there were two patients (5%) experienced knee pain after injection, which resolved within three days. [29 Level II-3] No treatment-related severe adverse event was reported. [29 Level II-3] An RCT by Conrozier T et al. (2016) reported that 8.25% of patients who had intra-articular injection of HA combined with mannitol had adverse reactions which were transient increase in pain in the knee following injection and occurrence of effusion in the target knee few days following injection. The three other reported AEs were transient headache, insomnia, and skin petechial rash. No serious AEs related to the injection were reported. [25 Level II-1]

In a retrospective cohort study by Guler O et al. (2015), it was reported that there was no major complication related to intraarticular injection of HA combined with mannitol detected during the study. [26 Level II-2] Temporary swelling occurred in eight knees in the intra-articular injection of HA combined with mannitol group. [26 Level II-2] Conrozier T et al. (2014) stated in their cross-sectional study that tolerability against the intra-articular injection of HA combined with mannitol was very good/ good in 86.4% of patients, moderate in 7.3% of patients and poor in 6.3% of patients with no significant difference when compared with the conventional intra-articular injection of HA. [34 Level III] Only one side effect reported which was a transient increase in hip pain after the injection for one to seven days. [34 Level III] Borrás-Verdera A et al. (2012) stated in their pre- and post-intervention study that there were no serious adverse events observed related to the intra-articular injection of HA combined with mannitol. Only mild side effects (local pain and swelling) were reported in four patients. [32 Level II-3]

5.4 COST / COST-EFFECTIVENESS ANALYSIS

There was no retrievable evidence on the cost-effectiveness of intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis.

The estimated market price of commercially available intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis is between RM 480 to RM 1,563 per injection, depending on the type or brand. For intra-articular injection of HA without the addition of sorbitol or mannitol for osteoarthritis, the estimated market price of commercially available injections is between RM 147 to RM 1,729 per injection, depending on the type or brand.

5.5 ORGANISATIONAL

5.5.1 Guidelines

There was no guideline retrieved which specifically addressed the use of intra-articular injection of HA with sorbitol or mannitol in osteoarthritis. However, there were guidelines issued by various international organisations with regards to the use of intra-articular injection of HA in general. Most guidelines found insufficient evidence to make a recommendation for or against the use of intra-articular HA for OA.[35] Some guidelines recommend the use of intra-articular injection of HA in certain situations or in certain age groups and certain OA grade.[35] The National Institute for Health and Care Excellence (NICE) and Osteoarthritis Research Society International (OARSI) recommended against the use of intra-articular injection of HA for knee OA.[35] In the 2019 American College of Rheumatology/Arthritis (ACR) Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee, intraarticular hyaluronic acid injections are strongly recommended against in patients with hip OA and conditionally recommended against in patients with knee and/or first carpometacarpal joint OA in the context of shared decision-making that recognises the limited evidence of benefit of the injection, when other alternatives have been exhausted or failed to provide satisfactory benefit.[36] An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) stated a weak recommendation to the use of intra-articular injection of HA in

patients who have contraindications to NSAIDs, or if the patient is still symptomatic despite the use of NSAIDs.[37] In the Malaysian Clinical Practice Guidelines (CPG) for Management of Osteoarthritis (Second Edition) 2013, it is stated that the CPG is unable to recommend the use of intra-articular injection of HA in the treatment of OA due to a lack of supporting evidence.[6]

5.6 LIMITATION

Our review has several limitations and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles and further limited the study numbers. Few RCTs and pre- and post- intervention studies included in this review had small sample size which limit the generalisability of the findings.

6.0 CONCLUSION

6.1 Effectiveness

Intra-articular injection of Hyaluronic Acid combined with Sorbitol

There was very limited fair level of retrievable evidence to suggest that IAHA + Sorbitol was associated with pain reduction, improvement in stiffness and function with no significant difference compared to conventional IAHA in patients with knee OA.

Intra-articular injection of Hyaluronic Acid combined with Mannitol

There was limited fair level of retrievable evidence to suggest that IAHA + Mannitol was associated with pain reduction, improvement in stiffness and function with no significant difference compared to conventional IAHA and placebo in one study, but clinically inferior to PRP in patients with knee OA. For hip OA and TMC OA, the evidence was insufficient to determine the effectiveness of IAHA + Mannitol in these populations.

6.2 Safety

There was no serious adverse event related to the intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis reported in the included studies.

6.3 Cost/Cost-effectiveness

There was no retrievable evidence on the cost-effectiveness of intra-articular injection of HA combined with sorbitol or mannitol for osteoarthritis.

6.4 Organisational

Guidelines

There was no guideline retrieved which specifically addressed the use of intra-articular injection of HA combined with sorbitol or mannitol in osteoarthritis. With regards to the

use of intra-articular injection of HA in general, most guidelines found insufficient evidence to make a recommendation for or against the use of intra-articular HA for OA. Some guidelines recommended its use in certain situations, age groups and OA grade. Guidelines from NICE, OARSI and ACR recommended against its use in OA.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

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: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1 Osteoarthritis/
2 (degenerative adj1 (arthritis or arthritides)).tw.
3 arthros*.tw.
4 osteoarthriti*.tw.
5 osteoarthros*.tw.
6 osteoarthrosis deformans.tw.
7 1 or 2 or 3 or 4 or 5 or 6
8 Hyaluronic Acid/
9 9004-61-9.tw.
10 9067-32-7.tw.
11 (hyaluronic adj1 acid).tw.
12 amo vitrax.tw.
13 amvisc.tw.
14 biolon.tw.
15 etamucine.tw.
16 healon.tw.
17 hyaluronan.tw.
18 (hyaluronate adj1 sodium).tw.
19 hyvisc.tw.
20 luronit.tw.
21 vitrax, amo.tw.
22 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
23 Sorbitol/
24 50-70-4.tw.
25 506t60a25r.tw.
26 Glucitol.tw.
27 Medevac.tw.
28 Sorbilax.tw.
29 Sorbitol.tw.
30 Yal.tw.
31 klysma sorbit.tw.
32 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 Mannitol/
34 3owl53l36a.tw.
35 Mannitol.tw.
36 Osmitrol.tw.
37 Osmofundin.tw.
38 33 or 34 or 35 or 36 or 37
39 Viscosupplementation/

40 viscosupplementation.tw.
41 Injections, Intra-Articular/
42 ((intra-articular or intraarticular or intra articular) adj1 injection*).tw.
43 39 or 40 or 41 or 42 or 22
44 43 and 32
45 43 and 38

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

Evidence Table : **Effectiveness/Safety**
Question : **Is intraarticular hyaluronic acid injection combined with sorbitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Cortet B, Lombion S, Naissant B et al. Non-Inferiority of a Single Injection of Sodium Hyaluronate Plus Sorbitol to Hylan G-F20: A 6-Month Randomized Controlled Trial. *Adv Ther*. 2021;38(5):2271-2283.	RCT **Aim:** To demonstrate the non-inferiority of Synolis VA (80 mg hyaluronic acid and 160 mg sorbitol) (IAHA + Sorbitol) to Synvisc-One (48 mg hylan GF-20) (IAHA) at Day 168 in terms of pain relief efficacy in patients with knee OA (Kellgren and Lawrence radiological stage II or III) in whom oral treatment with analgesics, NSAIDs or weak opioids provided insufficient clinical responses or were poorly tolerated. **Methods:** -Men and women aged between 45 and 80 years with knee OA based on the American College of Rheumatology classification with: -Radiographically defined osteoarthritis -Patients having had symptoms for at least 6 months prior to inclusion	II-1	202 patients were randomised: -predominantly female (66%). -median age of the whole population was 65 years, -No statistically significant differences between the two treatment groups were observed for any of the demographic criteria.	Synolis VA (80 mg hyaluronic acid and 160 mg sorbitol) (IAHA+Sorbitol)	Synvisc-One (48 mg hylan GF-20) (IAHA)	168 days	**Results:** <u>WOMAC pain score change</u> -The WOMAC pain score decreased in the two groups: - 29.2 ± 24.1 (SD) in the HA1 group and - 31.6 ± 25.5 (SD) in the HA2 group, confirming the non-inferiority of Synolis VA (P = 0.57 for the difference between groups). <u>Secondary end points (pain, function, stiffness, WOMAC total score, global pain satisfaction, investigator assessment of tx efficacy)</u> -Significant decrease in pain was seen at Day 7 and continued throughout the study with no significant difference between the groups. -Significant score improvement in stiffness and function as well as in the total score of WOMAC from baseline to Day 168 with no significant difference between the groups. -No statistically significant difference was observed in neither patient-assessed global pain satisfaction at Day 168 nor in the investigator assessment of treatment efficacy using Likert scale at Day 168 for both groups.	France

Evidence Table : **Effectiveness/Safety**
Question : **Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1.Cortet B, Lombion S, Naissant B et al. Non-Inferiority of a Single Injection of Sodium Hyaluronate Plus Sorbitol to Hylan G-F20: A 6-Month Randomized Controlled Trial. *Adv Ther*. 2021;38(5):2271-2283.	-Subjects who were intolerant to or for whom the treatment with analgesics and/or NSAIDs and/or weak opioids was insufficient. - Subjects with WOMAC pain C 40 mm on a visual analogue scale (VAS) ranging from 0–100 mm in the knee to treat and, if OA ws bilateral,\10 mm (VAS) on the contralateral knee. - Patients were randomized into two parallel groups at Day 0 and followed until Day 168. -Patients were randomized to one of the two treatment groups (HA1 or HA2) in a 1:1 ratio. - Two viscosupplements, one containing a solution of 80 mg HA-160 mg sorbitol (HA1) and the other containing 48 mg hylan GF-20 (HA2), in two parallel groups over a period of 24 weeks.						**Safety:** -Both products were well tolerated. - 86 patients reported AEs: 46 AEs in IAHA + Sorbitol group and 40 AEs in the IAHA group. Forty-six of those were related to the treatment (IAHA+Sorbitol n = 26/IAHA n = 20), with 37 related to underlying musculoskeletal disorders and 9 related to injection site abnormalities. -There was no statistically significant difference between the groups. **Conclusion:** Confirmed non-inferiority of IAHA+Sorbitol compared to IAHA at Day 168 according to the WOMAC pain score. Safety was satisfying and comparable in the two groups.	

Evidence Table : **Effectiveness/Safety**
Question : **Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Cortet B, Lombion S, Naissant B et al. Non-Inferiority of a Single Injection of Sodium Hyaluronate Plus Sorbitol to Hylan G-F20: A 6-Month Randomized Controlled Trial. *Adv Ther*. 2021;38(5):2271-2283.	-Randomization was performed per centre and by block of four under the responsibility of Sylia Stat, Bourg la reine, France -The primary end point was the evolution of the Western Ontario and McMaster University (WOMAC) pain index at D168 in the groups. -One of the secondary end points was the daily assessment of this index by the patient for 7 days following the injection and thereafter at Day 14. -The other secondary end points were the WOMAC pain, stiffness, function and total scores assessed at Day 28, Day 84 and Day 168. -At Day 168, efficacy and satisfaction were assessed by the evaluator and by the patient using a Likert scale (7 points). -Number of strict responders in each group was evaluated according to The Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative and the							

Evidence Table : **Effectiveness/Safety**
Question : **Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1.Cortet B, Lombion S, Naissant B et al. Non-Inferiority of a Single Injection of Sodium Hyaluronate Plus Sorbitol to Hylan G-F20: A 6-Month Randomized Controlled Trial. *Adv Ther*. 2021;38(5):2271-2283.	Outcome Measures in Rheumatology (OMERACT) criteria (OMERACTOARSI). -The per protocol (PP) population was used for the primary analysis.							

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013;63(9):445-449.	Pre and post-intervention study **Aim:** To extend established knowledge on the safety and efficacy of the GO-ON ® matrix product in a setting representative of routine clinical practice. **Methods:** -Study was performed at 398 recruiting centres in Germany between May 2011 and March 2012 -Enrolled patients were interviewed on Day 1 for screening and the collection of the patient's disease diagnosis, medical history (including disease duration), and prior/concomitant medication data, as well as identification of the joint to be treated. -Prior to the first injection on Day 1, the patient assessed their pain and functional impairment due to OA.	II-3	1147 patients (43.5 % male, 53,5 % female, 3 % missing) aged on average 63.3 years with osteoarthritis were enrolled in 398 centres -The most commonly treated joint was the knee (92.9 %) with a Kellgren-Lawrence classification of Grade I (6.7 %), Grade II (31.4 %), Grade III (48.0 %), and Grade IV (13.9 %). -Most patients (58–66 %, imputing for missing data) received 1 injection, 29–40 % received 3 injections.	Intraarticular injection of hyaluronic acid/sorbitol formulation (GO-ON® matrix)		Six months	**Results:** **Pain** -the mean change in pain due to OA was a reduction of 56.5 % from baseline (2.61 ± 0.80) to 6 months (1.07 ± 0.86). -The proportion of patients with severe or very severe pain due to OA reduced substantially from 56.2 % at baseline to 6.2 % after 3 months and 5.9 % 6 months after the first injection -Similarly, the proportion of patients with no pain, or only mild pain increased from 6.8 % at baseline to 66.8 % after 3 months, and 67.1 % 6months after the first injection. -Statistically significantly greater mean reductions in pain for patients receiving 3 injections (1.65 points) vs. only 1 injection (1.44 points). -No statistical differences were apparent based upon Kellgren-Lawrence grading alone although the difference in scoring points between 1 and 3 injections was higher in patients with higher grading. **Functional impairment** -After 6 months, the mean improvement in functional impairment was 0.98 points (± 1.05). -The proportion of patients with severe or very severe functional impairment due to OA reduced from 29.1 % at baseline to 3.6 % after 3 months, and 3.9 % six months after the first injection.	Germany

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013;63(9):445-449.	-At both 1 and 2weeks following the first injection patients attended the clinic for additional treatment visits. -Patient's assessment of pain and functional impairment due to OA (prior to injection) as well as independent assessments of global efficacy from the patient and investigator were collected prior to treatment. -The GO-ON ® matrix injection was then administered at the investigator's discretion. -Thereafter, at weeks 4, 12 and 24, patients attended the clinic for assessment of their pain and functional impairment due to OA, as well as independent patient and investigator assessments of global efficacy. -Patients were actively questioned regarding possible adverse reactions at all visits.		-Most patients (68.0 %) did not receive concomitant medications for their OA, of those who did, 27.3 % received only 1 concomitant medication. -The most common concomitant medications being acetic acid derivatives (37.4 %) or propionic acid derivatives (29.1 %).				-Proportion of patients with mild or no impairment improved from 28.9 % at baseline to 66.4 % after both 3 months and 6 months after the first injection. -After 6 months, the majority of patients reported a 2-class improvement (18.0 %), 1-class improvement (30.9 %), or no change (27.3 %) in functional impairment. -In all, only 3.5 % of patients experienced a worsening in functional impairment. -Subgroup analyses revealed statistically greater improvements in functional impairment for patients receiving 2 (1.44 points) or 3 injections (1.13) vs. only 1 injection (0.89). -No statistical differences were apparent based upon Kellgren-Lawrence grading. -At 1-week after treatment initiation, 61.6 % of patients and 51.0 % of investigators reported the patient's condition to be better or much better. -This improved to 77.7 % of patients vs. 78.5 % of investigators at 3 months, and 72.5 % of patients vs. 73.0 % of investigators at 6 months after treatment initiation. -At the final assessment the investigator rated the treatment success as better than conventional HA therapies for 48.9 % of patients and equivalent for 33.9 %.	

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013;63(9):445-449.	-Patient subjective assessments of pain and functional impairment due to OA were performed prior to receiving the GO-ON ® matrix injection, each using a 5-point Likert scale from none (0), through mild (1), moderate (2), severe (3), to very severe (4). -Global subjective assessments of the OA treatment efficacy were performed independently by both the patient and the investigator using a 5-point scale from much better, through better, no change, worse, to much worse. -A final subjective assessment of therapy success was performed by the investigator rating the GO-ON ® matrix as better, equal, or worse than conventional hyaluronic acid.						**Adverse reactions** -22 patients reported 24 ARs, all of which were in the SOC musculoskeletal and connective tissue disorders. -The most commonly reported AR was injection site joint pain (n = 15). -Reactions to the injections were more common following the first injection than subsequent treatments. The most common reaction following each injection with the GO-ON ® matrix was pain in joint; this was more common after the first injection (n = 81, 7.1 %) than after subsequent injections (2nd injection:n = 17, 3.5–4.4 % [worst case-best case]; 3rd injection: n = 16, 3.5–4.8 %). After the first injection only, swelling (n = 14, 1.2 %) and effusion (n = 12, 1.0 %) also had an incidence ≥ 1.0 %. -No infections of treated joints were reported during the course of the trial. **Conclusion:** GO-ON matrix ® (IAHA + Sorbitol) treatment is effective and well tolerated in the treatment of symptoms due to osteoarthritis.	

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Heisel, J.Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit einer intraartikulären Behandlung der Gonarthrose. Deutscher Ärzte-Verlag | OUP | 2012; 1 (6).	Pre and post interventional study **Aim:** To gain further knowledge on the efficacy and tolerability of injections of high-dose sodium hyaluronate (hyaluronic acid) and sorbitol. **Methods:** -All participants in the study received three intra-articular injections of the preparation into the affected knee joint at intervals of one week. - Patients had to be at least 18 years old and have radiologically confirmed osteoarthritis of at least grade I (Kellgren- Lawrence) to be included in the study. - Patients were not included in the study if they were receiving (or had received immediately beforehand) another intra-articular treatment (e.g. corticosteroids). - The data were analysed using descriptive statistical methods.	II-3	101 patients with long-standing osteoarthritis of the knee (mean age 58 years, ca. 55% female) were treated with three intra-articular (i.a.) injections at weekly intervals of a new medication (high-dose sodium hyaluronate [hyaluronic acid] and sorbitol [GO-ON matrix]*).	2 ml pre-filled syringe contains 40 mg HA (2% gel), 80 mg of sorbitol & buffered saline. (IAHA+Sorbitol)		24 weeks	**Results:** -At baseline: 4% were pain-free, while 21.8% complained severe or very severe pain. -The proportion of pain-free patients increased steadily after each of the three injections. -After the first injection, 16.8% of the patients were pain-free, and 40.6% were pain-free 24 weeks after treatment -At the same time, the proportion of patients with moderate, severe or very severe pain decreased significantly during treatment. -The proportion of patients with severe or very severe pain decreased from 21.8% to 5% after the first injection, and 74.3% of the patients reported that their pain was reduced at 24 weeks after the start of treatment. -At the same time, the extent of functional impairment was also reduced. -14.9% of patients complained of severe or very severe impairment before treatment, but only 4% complained of this degree of impairment after the first injection. -The proportion of patients with no functional deficit increased from 31.7% to 51.5%. 24 weeks after the start of the injection treatment, 45.5% of patients reported an improvement with respect to baseline values.	Germany

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with sorbitol effective and safe for osteoarthritis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Heisel, J.Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit einer intraartikulären Behandlung der Gonarthrose. Deutscher Ärzte-Verlag | OUP | 2012; 1 (6).							-The patients and their treating doctors assessed the overall efficacy of the injections in a very similar way. -The proportion of patients who reported improvement increased from 64.4% one week after the first injection to 87.1% a week after the third injection, while assessment by the doctors improved from 57.4% to 82.2%. -There were no local or systemic adverse effects.	

Evidence Table : **Effectiveness / Safety**
Question : **Is intraarticular hyaluronic acid combined with mannitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Maheu E, Avouac B, Dreiser RL et al. A single intra-articular injection of 2.0% non-chemically modified sodium hyaluronate vs 0.8% hylan G-F 20 in the treatment of symptomatic knee osteoarthritis: A 6-month, multicenter, randomized, controlled non-inferiority trial. PLoS One. 2019;14(12):e0226007.	RCT **Aim:** To demonstrate the non-inferiority of a single intra-articular injection of 2.0% non-chemically modified sodium hyaluronate (IAHA + Mannitol) vs 0.8% hylan G-F 20 (IAHA) in symptomatic knee osteoarthritis. **Methods:** -Participants were recruited in private medical practices in France. -Eligible patients were men and women (aged 40 to 85 years) with primary knee OA - Patients eligible at screening entered a washout period for analgesics and NSAIDs lasting 2 to 5 days, depending on the drug. -They were consecutively randomised at baseline (D0) to receive either a single intra-articular injection of SH (test product) or a single intra-articular injection of hylan G-F 20 (control) within 2 days after randomisation.	II-1	292 patients randomised: 144 patients in the IAHA + Mannitol group and 148 patients in the IAHA group	Ostenil1 Plus (IAHA + Mannitol)	Synvisc-One1 (IAHA)	6 months	**Results:** -WOMAC A change at 6 months was -34.3 mm (95% CI: -37.8, -30.8) and -36.2 mm (95% CI: -40.3, -32.1) for the SH and hylan G-F 20 patients, respectively (P = 0.5). -The intergroup difference was -2.9 mm (95% CI: -7.9, 2.2). - Significant improvements in stiffness and function were noted in both groups after treatment (*P* <0.001), which was maintained up to the end of the study. Safety: -A total of 31.3% of the injected patients reported a treatment-emergent adverse event, including injection site reactions (pain, inflammation or effusion) which occurred in 8.5% of the IAHA + Mannitol patients vs 13.0% of the IAHA patients. -No serious reactions were reported **Conclusion:** This clinical trial demonstrated the non-inferiority of a single intra-articular injection of IAHA + Mannitol vs IAHA on the WOMAC A change from baseline at 6 months.	France

Evidence Table : **Effectiveness/Safety**
Question : **Is intraarticular hyaluronic acid combined with mannitol effective and safe for osteoarthritis?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Maheu E, Avouac B, Dreiser RL et al. A single intra-articular injection of 2.0% non-chemically modified sodium hyaluronate vs 0.8% hylan G-F 20 in the treatment of symptomatic knee osteoarthritis: A 6-month, multicenter, randomized, controlled non-inferiority trial. PLoS One. 2019;14(12):e0226007.	-Patients were then examined for efficacy and safety at 30, 90 and 180 days (D30, D90, D180). -Patients who prematurely discontinued were not replaced. - Subjects were excluded if their knee OA resulted from a trauma or was predominantly of patellofemoral origin. -Further exclusion criteria comprised ; a.excessive varus/valgus knee deformity b.inflammatory/metabolic rheumatic diseases, obesity, c.history of injury to the studied knee in past 6 months, d.lower limb pain other than knee OA, and e. severe disease likely to interfere with trial assessments. -Patients with the following treatments were also excluded: intra-articular HA injection in the studied knee within the previous 6 months, intra-articular corticosteroid injection in the studied knee within the previous two months,							

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2. Barac, Branko & Damjanov, Nemanja & Zekovic, A. The New Treatment Approach In Knee Osteoarthritis: Efficacy Of Cellular Matrix Combination Of Platelet Rich Plasma With Hyaluronic Acid Versus Two Different Types Of Hyaluronic Acid (Ha). Annals of the Rheumatic Diseases. 2019: 78. 500.1-500.	RCT **Aim:** To compare the efficacy of intra-articular injections of platelet rich plasma (PRP) combined with hyaluronic acid (HA) prepared with the Cellular Matrix device versus IA injections with two different types of hyaluronic acid for treatment of knee osteoarthritis. **Methods:** -53 patients (90 knees) with knee osteoarthritis, divided in 3 groups: -PRP+HA -IAHA -IAHA + Mannitol - All groups were homogeneous eg.gender, age and Kellgren Lawrence scale (I to III). -For all patients visual analog pain scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), The International Knee	II-2	53 patients (90 knees) with knee osteoarthritis, divided in 3 groups: a.19 patients (30 knees) treated with 3 IA injections, one every second week, of PRP-HA combination. b. 19 patients (30 knees) was treated with 3 weekly IA injections of 2% noncross-linked sodium HA (IAHA) c.15 patients (30 knees) treated with 3 weekly IA injections of 2% non-cross-linked sodium HA with mannitol (IAHA + Mannitol). -No statistically significant differences for: VAS, WOMAC, IKDC and KOOS scores between 3 groups at baseline ($p>0.05$).	3 weekly IA injections of 2% non-cross-linked sodium hyaluronate with mannitol (IAHA + Mannitol)	a.3 IA injections, one every second week, of Cellular Matrix PRP-HA combination. b. 3 weekly IA injections of 2% noncross-linked sodium hyaluronate (IAHA)	12 months	**Results:** After 2 months, there were statistically significant differences in PRP-HA Group when compared to IAHA and IAHA + Mannitol groups in VAS, WOMAC, KOOS and IKDC scores $p<0.05$. -Highly statistically significant differences ($p<0.01$) in PRP-HA Group when compared to IAHA and IAHA + Mannitol groups in VAS, WOMAC, KOOS and IKDC score 6 months after the last injection. -In both groups of patients treated with hyaluronic acid, a deterioration of values for VAS, WOMAC, KOOS and IKDC score was seen at 12 months in relation to values at 6 months. -The PRP-HA treated group showed statistically significant improvement ($p<0.05$) of the cartilage thickness after 2, 6 and 12 months in the medial and highly statistically significant improvement ($p<0.01$) in the lateral segments of knee cartilage in comparison to baseline values. **Safety:** -No single serious adverse events were reported in patient treated with PRP-HA combination. -In 5 patients treated with HA, 2 in IAHA group and 3 in IAHA + Mannitol group, mild inflammatory reactions, with redness on treated spot, were recorded which lasted for a maximum of 12 hours.	-Small sample size -Serbia

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3. Dauvissat J, Rizzo C, Lellouche H et al. Safety and Predictive Factors of Short-Term Efficacy of a Single Injection of Mannitol-Modified Cross-Linked Hyaluronic Acid in Patients with Trapeziometacarpal Osteoarthritis. Results of a Multicentre Prospective Open-Label Pilot Study (INSTINCT Trial). Clin Med Insights Arthritis Musculoskelet Disord. 2018;11:1179544118782901.	Pre and post-intervention study **Aim:** To assess safety and search predictive factors of efficacy of a single intra-articular injection of a mannitol-modified hyaluronic acid (IAHA + Mannitol) viscosupplement, in patients having trapeziometacarpal (TMC) osteoarthritis (OA). **Methods:** -Patients with symptomatic TMC OA, not sufficiently relieved by conventional first-line treatments (analgesics and/or NSAIDs and/or thumb splint), were recruited between March 2016 and February 2017. -All underwent X-rays performed according to the Kapandji incidences showing evidence of rhizarthrosis (joint space narrowing and/or osteophyte).	II-3	A total of 122 patients were included and 120 (98%) were assessed at 3 months. - 93 participants (76%) were women, the average age was 60 years, and the average disease duration was 36 months. - 23% of the TMC OA were grade 1 according to Dell classification, 36.8% grade 2, 36.8% grade 3, and 3.5% grade 4. - The injection was performed using fluoroscopy in 83% and by ultrasound in 17% of cases	Intra-articular injection of a mannitol-modified hyaluronic acid (IAHA + Mannitol)		3 months	**Results:** -At D0, the average (SD) pain level was 6.5 ± 1.6 without significant difference between grades (*P* = 0.21). -At day 90, pain decreased from 6.5 ± 1.6 to 3.9 ± 2.5 (difference −2.7 ± 2.5; −42%; *P* < .0001) without significant difference between Dell grade (*P* =0.055) -In multivariate analysis, no predictor of response was identified. -.69% of patients estimated the treatment as effective (21% very effective, 31% effective, 17% slightly effective) and 21% rated it ineffective. -In 78% of cases, analgesic consumption decreased by more than 50% and in 66% of cases by more than 75%. -There was no safety issue. All adverse events (11%) were transient increase in pain during or following IAHA + Mannitol administration and resolved without sequel within 1 to 7 days. **Conclusion:** This study suggests that a single course of IAHA + Mannitol injection is effective in relieving pain in patients with TMC OA, without safety concern. Patients with advanced stage of OA benefit the treatment as much as those with mild or moderate OA.	France

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Monet M, Bozgan AM, Conrozier T. Safety and Efficacy of Single Intra-Articular Injection of a Cross-Linked Hyaluronic Acid/Mannitol Formulation [Happycross®] in knee Osteoarthritis Results of a Prospective Observational Study in Daily Practice Conditions.Ortho & Rheum Open Access 2017; 5(3): 555664.	Pre- and post-intervention study **Aim:** To assess both safety and efficacy of a single intra-articular injection of a cross-linked hyaluronic acid combined with mannitol (IAHA + Mannitol) in patients with symptomatic knee osteoarthritis. **Methods:** **-**Clinical and radiological data of 53 consecutive patients with symptomatic knee OA, treated between January and June 2016 with a single intra-articular injection of IAHA + Mannitol were analysed. -Efficacy endpoints included the changes over time in the normalized (0-10) WOMAC pain, function and total and the patient's global assessment (PGA). Patient Acceptable Symptom State (PASS) and Minimum Clinically Important Improvement (MCII) were calculated	II-3	53 patients with knee OA	intra-articular injection of a cross-linked hyaluronic acid combined with mannitol (IAHA + Mannitol)		18-32 weeks	**Results:** -No patient was lost to follow-up. -At baseline the mean WOMAC pain sub-score and PGA were 4.6 (1.2) and 6.0 (1.1) respectively. -The average decrease of WOMAC score over the 6 month follow-up was > 50%, versus baseline values, for both pain and function (P<0.0001). -At month 6, 82% of patients were PASS + and 86.8% had experienced improvement > MCII threshold. -Three patients experienced local adverse events (increase of knee pain) after injection that resolved within 3 days. **Conclusion:** In daily practice conditions, treatment with a single IA injection of HAnox-M-XL alleviates by more than 50% knee OA symptoms, over 6 months, in a large majority of patients, without safety concern.	-Small sample size -France

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5. Henrotin Y, Berenbaum F, Chevalier X et al. Reduction of the Serum Levels of a Specific Biomarker of Cartilage Degradation (Coll2-1) by Hyaluronic Acid (KARTILAGE® CROSS) Compared to Placebo in Painful Knee Osteoarthritis Patients: the EPIKART Study, a Pilot Prospective Comparative Randomized Double Blind Trial. BMC Musculoskelet Disord. 2017;18(1):222.	RCT **Aim:** To evaluate the effects on Coll2-1, a biomarker of cartilage degradation, of an intra-articular injection of IAHA + Mannitol versus placebo in patients suffering from knee pain. Clinical efficacy and tolerance for the product were investigated as well as the correlation between Coll2-1 and clinical parameters. **Methods:** -81 patients with symptomatic knee osteoarthritis were randomised to IAHA + Mannitol (KARTILAGE® CROSS, 16 mg/ml, one single injection of 2.2 mL; IAHA) or saline solution. -Primary outcome was the percentage of patients with a reduction of at least 10 nmol/l of serum Coll2-1 between visit (D-10) and D90 (3 months after injection).	II-2	81 patients were randomised: 40 in the treatment group and 41 in the saline solution group. -Four patients finished prematurely: one (2.5%) from the treatment group due to AE, 3 (7.3%) from the saline solution group (one for AE, one for AE and inefficacy, one for loss of follow up at D180). - Five patients in the treatment group (17%) and 10 (30%) in the saline solution group presented a major deviation to protocol. -The ITT and FAS populations contained 81 patients (40 in the treatment group and 41 in the saline solution group) and the PP population	KARTILAGE® CROSS (IAHA + Mannitol)	Saline injection	6months	**Results:** -Percentage of patient with a reduction of at least 10 nmol/l of serum Coll2-1 between D-10 and D90 was 52.5% in the treatment group and 31.7% in the placebo group (P = 0.0580). - No statistically significant difference was observed between groups regarding the change in function (LI) or pain (VAS). -There was also no difference regarding the OMERACT-OARSI responders and the patient global assessment on disease activity. - No significant difference was observed between the 2 groups regarding the consumption of acetaminophen (50.0% vs 53.7% between D0 and D30, 55.0% vs 52.5% between D30 and D90 and 35.0% vs 47.4% between D90 and D180 for IAHA and saline solution respectively) and or NSAIDs (7.5% vs 7.3% between D0 and D30, 7.5% vs 7.5% between D30 and D90 and 10.0% vs 2.6% between D90 and D180 for IAHA and saline solution respectively). Safety: - Thirty AEs were reported in 29 patients among 81 (35.8%) during the study, 14 in the IAHA group and 15 in the saline solution group. -Two AEs were considered attributable to the product, one joint effusion in the treatment group and one inflammation at the injection site in the	-Small sample size -Belgium

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6. Duymus TM, Mutlu S, Dernek B, Komur B, et al. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. 2017;25(2):485-492.	RCT **Aim:** To compare the efficacy of treatment in three groups of patients with knee osteoarthritis (OA) given an intra-articular injection of platelet-rich plasma (PRP), hyaluronic acid (IAHA + Mannitol) or ozone gas. **Methods:** -102 patients with mild–moderate and moderate knee OA who presented at the polyclinic with at least a 1-year history of knee pain and VAS score ≥4 wer randomly separated into three groups. -Group 1 (PRP group) received intra-articular injection of PRP × 2 doses, Group 2 (IAHA + Mannitol group) received a single dose of HA, and Group 3 (Ozone group) received ozone × four doses. -Weight-bearing anteroposterior–lateral and Merchant's radiographs of both knees were evaluated. WOMAC and VAS scores were applied to all	II-2	102 patients with mild to moderate knee OA	Ostenil Plus® syringe is a pre-filled syringe containing 40 mg of fermentative HA and 10 mg of mannitol (IAHA + Mannitol group)	a.intra-articular injection of PRP × 2 doses, b. ozone × four doses.	12 months	**Results:** At the end of the 1st month after injection, significant improvements were seen in all groups. -In the 3rd month, the improvements in WOMAC and VAS scores were similar in Groups 1 and 2, while those in Group 3 were lower ($p < 0.001$). -At the 6th month, while the clinical efficacies of PRP and HA were similar and continued, the clinical effect of ozone had disappeared ($p < 0.001$). -At the end of the 12th month, PRP was determined to be both statistically and clinically superior to HA ($p < 0.001$). **Conclusion:** In the treatment of mild–moderate knee OA, PRP was more successful than IAHA + Mannitol and ozone injections, as the application alone was sufficient to provide at least 12 months of pain-free daily living activities.	-Turkey

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7. Conrozier T, Bozgan AM, Bossert M, Sondag M, Lohse-Walliser A, Balblanc JC. Standardized Follow-up of Patients with Symptomatic Knee Osteoarthritis Treated with a Single Intra-articular Injection of a Combination of Cross-Linked Hyaluronic Acid and Mannitol. Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:175-179.	Pre- and post-intervention study **Aim:** To obtain data, in daily practice conditions, on safety and efficacy of a double dose (4.4 mL) of HAnox-M-XL (IAHA + Mannitol) administered through a single injection in patients with symptomatic KOA. **Methods:** -Data of 40 consecutive patients, 29 women and 11 men, who were prospectively followed up for 6 months, using a standardized procedure, were retrospectively analysed. -All patients have received a single intra-articular injection of HAnox-M-XL (4.4 mL), viscosupplement made of a cross-linked HA (16 mg/mL) + mannitol (35 mg/mL), in the target knee. -The primary outcome was safety.	II-3	40 patients: -29 women -11 men With symptomatic knee OA -Mean (SD) age was 60.7 (13.9) years, and mean BMI was 28.6 (5.0). -Kellgren–Lawrence radiological grade was I/II and III/IV in 13 and 27 of the subjects, respectively.	Intraarticular HA with mannitol		6 months	**Results;** -The average WOMAC pain and WOMAC total scores at baseline were 21.5 (9.8) and 89.9 (42.8), respectively. -Thirty-nine patients completed the follow-up. -IAHA + Mannitol was well tolerated; two patients experienced knee pain after injection, which resolved within three days. -No treatment-related severe adverse event was reported. -Mean (SD) variations in WOMAC pain and WOMAC total scores were −8.2 (8.9) and −38.4 (35.6), respectively, at month 6 (P = 0.001). -PGA decreased from 5.5 (2.0) to 3.0 (2.2) (P = 0.006). -Efficacy was rated as *good or very good* in 76.9% of the cases. -Most of the regular analgesics users decreased their consumption. **Conclusion:** Treatment with one injection of 4.4 mL IAHA + Mannitol is effective to alleviate KOA symptoms over six months, without safety concern. Controlled trials are needed to confirm these findings.	-Small sample size -France

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8. Conrozier T, Eymard F, Afif N, Balblanc JC, Legré-Boyer V, Chevalier X; Happyvisc Study Group. Safety and efficacy of intra-articular injections of a combination of hyaluronic acid and mannitol (HAnOX-M) in patients with symptomatic knee osteoarthritis: Results of a double-blind, controlled, multicenter, randomized trial. Knee. 2016;23(5):842-848.	RCT **Aim:** To assess the efficacy of three weekly injection of HAnOX-M (IAHA + Mannitol) in patients with symptomatic knee OA, by comparing both its efficacy and safety to that of a proved effective and well-tolerated HA viscosupplement **Methods:** -Patients with symptomatic knee OA, with radiological OARSI grades 1 to 3, were enrolled -Patients were randomised to three intra-articular injections at weekly intervals, of either HAnOX-M made of a combination of HA (MWone to 1.5MDa, 31 mg/2ml) and mannitol (70 mg/2 ml) or Bio-HA (MW2.3 to 3.6 MDa, 20 mg/2 ml). -Primary outcome was six-month change in WOMAC pain subscale (0 to 20).	II-2	222 subjects. -109 were randomized to receive HAnOX-M (IAHA + Mannitol) and 113 to receive Bio-HA (IAHA)	HAnOX-M (IAHA + Mannitol)	Bio-HA (IAHA)	6 months	**Results:** -Mean (SD) variations in WOMAC pain score were −4.4 (3.8) and −4.5 (4.3) mm, for IAHA + Mannitol and IAHA respectively, demonstrating non-inferiority. - Average six-month change in the walking pain was −2.9 (2.8) for IAHA + Mannitol and −2.6 (2.4) for IAHA (p=0.49). -About 82.6% of patients considered there were symptoms improvements at three months and 85.5% considered there were symptoms improvements regardless the treatment groups. -about 58.2% of patients had reduction in analgesic intake between six months with 49.2% in the IAHA + Mannitol group compared to 56.3% in the conventional IAHA group with no significant difference between groups (p=0.73). -Both groups showed similar percentages of patients who completely stopped analgesics intake with about 23.8% of patients in IAHA + Mannitol group compared to 28.8% in conventional IAHA group (p=0.72). **Safety:** 8.25% of patients in IAHA + Mannitol had adverse reactions which were transient increase in pain in the knee following injection and occurrence of effusion in the target knee few days following injection.	France

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8. Conrozier T, Eymard F, Afif N et al. Happyvisc Study Group. Safety and efficacy of intra-articular injections of a combination of hyaluronic acid and mannitol (HAnOX-M) in patients with symptomatic knee osteoarthritis: Results of a double-blind, controlled, multicenter, randomized trial. Knee. 2016;23(5):842-848.	-Sample size was calculated according to a non-inferiority margin of 1.35. -Secondary endpoints included six-month change in function and walking pain, analgesic consumption and safety.						The three other reported AEs were transient headache, insomnia, and skin petechial rash. No serious AEs related to the injection were reported. **Conclusion:** Treatment with IAHA + Mannitol is effective to alleviate knee OA symptoms and to improve joint function over six months, with similar safety than conventional HA viscosupplement	

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9. Eymard F, Bossert M, Lecurieux R et al. (2016) Addition of Mannitol to Hyaluronic Acid may Shorten Viscosupplementation Onset of Action in Patients with Knee Osteoarthritis: Post-Hoc Analysis of A Double-blind, Controlled Trial. J Clin Exp Orthop 2:21.	Retrospective analysis / cross-sectional study **Aim:** To compare both efficacy and safety of a 3 weekly injection regimen of HANOX-M (HAppyVisc®, LABRHA SAS, Lyon, France), combining sodium hyaluronate (1–1.5 MDa, 31 mg/2 ml) with mannitol 3.5%, to BioHA (Euflexxa®, Ferring Pharmaceuticals, Parsippany, USA, 2.4-3.6 MDa, 20 mg/2 ml), in patients with symptomatic knee OA. **Methods:** -Males and females, aged 40–85 years, fulfilling the ACR criteria for knee OA who failed to respond or were intolerant to analgesics and/or NSAIDs or weak opioids and who had self-assessed their walking pain from 3 to 8 on a 11-point Likert scale (0-10) at baseline were included.	III	205 patients constituted the ITT population including 103 patients in the HAnox-M group and 102 in the Bio-HA group.	HANOX-M (IAHA + Mannitol)	BioHA (IAHA)	26 weeks	**Results:** -Both groups were not statistically different at baseline and month 6. -The median WOMAC pain score at baseline was 9 in both groups. - the median (range) of the WOMAC pain sub-score was 9.0 (4-19), 6.0 (0-19) and 5.0 (0-15) in the IAHA + Mannitol at baseline, week two and week three post injection respectively, compared to 9.0 (2-18), 7.0 (0-16) and 6.0 (0-14) in the conventional IAHA group showing a decrease in pain score in the treatment group however the difference was not statistically significant. -The average decrease of pain (SD) was found greater in the IAHA + Mannitol group compared to the conventional IAHA group at both week two: -3.0 (3.6) versus -1.9 (3.1) respectively, p=0.10 and at week three: -4.2 (3.2) versus -2.8 (2.6) respectively, (p=0.048) in patients with more severe joint space narrowing. **Conclusion:** In patients with symptomatic knee osteoarthritis, addition of mannitol to HA may shorten the onset of action of viscosupplementation, chiefly in patients with advanced stage of the disease.	

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9. Eymard F, Bossert M, Lecurieux R et al. (2016) Addition of Mannitol to Hyaluronic Acid may Shorten Viscosupplementation Onset of Action in Patients with Knee Osteoarthritis: Post-Hoc Analysis of A Double-blind, Controlled Trial. J Clin Exp Orthop 2:21.	-Patients were randomized to one of the following treatment groups: HAnox-M (IAHA + Mannitol) or Bio-HA (IAHA) in a 1:1 ratio by blocks of 4 treatments, balanced 2:2. -Both viscosupplements were supplied in 2 ml syringes containing 2 ml of HA solution and were administered, one week apart, 3 consecutive weeks, into the target knee by an experienced physician who was unblinded to treatment and different from the clinical evaluator. -The patient and the clinical evaluator were both blinded to treatment throughout the follow-up. -The primary efficacy outcome was the variation, between baseline and the last follow-up visit at week (W)26, in the WOMAC A pain sub-score measured on a 5 point Likert scale (5 pt-LS: 0=none, 1=mild, 2=moderate, 3=evere, 4=extreme; total score ranging 0-20).							

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10.Guler O, Mutlu S, Isyar M et al. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25(3):509-513.	Retrospective cohort study **Aim:** To compare short-term clinical outcomes between intraarticular platelet-rich plasma (PRP) and hyaluronic acid (HA) treatments in early-stage knee OA patients. **Methods:** -Data of knee OA patients in stage 1 / stage 2 Kellgren–Lawrence classification and underwent intraarticular PRP or HA treatment in between February 2011 and November 2012, obtained retrospectively from hospital records. -Patients were evaluated using the KSS and the VAS scoring system before treatment and at the second and sixth months of treatment. -Demographic characteristics, complications and adverse events during treatment were recorded.	II-3	63 patients (86 knees) were in the IAHA + Mannitol group and 69 patients (89 knees) were in the PRP group. -Two groups were compared in terms of VAS and KSS scores before and after treatment. - mean age of 55.06 ± 8.41 years. - No significant difference was determined between the treatment groups in terms of gender, age, body mass index (BMI), distribution among stages, and unilateral/bilateral involvement.	Osteonil_ plus 40 mg/2.0 mL (IAHA + Mannitol)	PRP	6 months	**Results:** - PRP group had significantly higher KSS scores at the post-treatment second month and sixth month. -Change in KSS score over time and the difference between treatment groups in terms of change in KSS score over time were significant (p<0.001 and p<0.001, respectively). - Increase in KSS score from baseline to post-treatment second month was significant (p<0.001). -This increase was higher in the PRP group than in the IAHA + Mannitol group (difference between the scores in the IAHA + Mannitol group: 10.01 ± 0.11; difference between the scores in the PRP group: 17.61 ± 5.61; p<0.001). - Increase in KSS score from post-treatment second month to post-treatment sixth month was significant (p<0.001). -This increase was higher in the PRP group than in the IAHA + Mannitol group (difference between the scores in the HA group: 8.78 ± 3.28; difference between the scores in the PRP group: 10.85 ± 5.17; p = 0.008). - Decrease in VAS scores from baseline to post-treatment second month was significant (p\0.001). -The decrease was higher in the PRP group than in the IAHA + Mannitol group (difference between the scores in the IAHA + Mannitol group: -1.83 ± 0.56; difference between the scores in the PRP group: -3.01 ± 1.01; p\0.001).	Turkey

Evidence Table : Effectiveness/Safety
Question : Is intraarticular hyaluronic acid combined with mannitol/sorbitol effective and safe for osteoarthritis?

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10.Guler O, Mutlu S, Isyar M et al. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25(3):509-513.							-Decrease in VAS score from post-treatment second month to post-treatment sixth month was significant (p\0.001). This decrease did not differ in the groups (difference between the scores in the HA group: -1.07 ± 0.61; difference between the scores in the PRP group: -1.10 ± 1.07; p = 0.161). -Any intraarticular injection-related major complication (infection, deep venous thrombosis, muscular atrophy, etc.) was not detected in any of the patients over the course of treatments. -Temporary swelling occurred in 5 knees in the PRP group and in 8 knees in the HA group **Authors' Conclusion:** PRP appears to be an appropriate option for intraarticular treatment in patients with early-stage knee osteoarthritis.	

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11. Conrozier, Thierry & Bossert, M. & Walliser-Lohse, A. & Sondag, M. & Balblanc, J.C.. (2014). Viscosupplementation with HANOX-M-XL is effective in moderate hip osteoarthritis but is not an alternative to hip joint surgery in patients with severe disease. Results of a clinical survey in 191 patients treated in daily practice. EMJD. 2. 49-55.	Cross-sectional study **Aim:** To assess efficacy of a single injection of HANOX-M-XL (IAHA + Mannitol) in patients with symptomatic hip OA, by comparing those in who viscosupplementation was the last resort before total hip replacement and those with a less severe symptomatology, irrespective to the radiological grade of disease. **Methods:** -191 patients who received a single injection of HANOX-M-XL into the hip joint within the 6 previous months were contacted by phone to answer questionnaires. -1 patient refused -Demographic data, imaging guidance, pain score, patients' self evaluation of efficacy, satisfaction and tolerability were obtained. -Patients were classified into two groups; a. those for which the viscosupplementation	III	191 patients with symptomatic hip OA -patients mean age was 65.2	single injection of HANOX-M-XL (IAHA + Mannitol)			**Results:** -Percentages of patients: Very satisfied 24.6% Satisfied 27.7% Not really satisfied. 22.5% Not satisfied at all 25.1% with treatment -The efficacy was considered as very good/good in 86.4%, moderate in 23.6%, and poor in 24.6% -Efficacy was unrelated to age, gender, and guidance but was highly correlated to pain on likert scale. (P<0.0001) -Efficacy was significantly different with regard to the clinical severity 66.6& of the NS group patients were satisfied with the treatment vs only 25% in THA group (P<0.0001). -In satisfied patients, the decrease of analgesics/NSAIDs consumption was >75% in 60.5% of cases. Safety: -Tolerability against IAHA + Mannitol was very good/ good in 86.4% of patients, moderate in 7.3% of patients and poor in 6.3% of patients with no significant difference when compared with the conventional intra-articular injection of HA. -Only one side effect reported which was a transient increase in hip pain after the injection for one to seven days.	France

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12. Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J et al. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period]. Rev Esp Cir Ortop Traumatol. 2012;56(4):274-80.	Pre and post intervention study **Aim:** To evaluate the safety and efficacy of a single intra-articular injection of 2% hyaluronic acid (HA) + mannitol in symptomatic knee osteoarthritis (KOA). **Methods:** - A total of 80 patients (aged 40 years or older) diagnosed with class III knee osteoarthritis according to the American College of Rheumatology (ACR) criteria were included in the study. - Inclusion criteria for subjects were: at least class III joint functionality in the knee to be treated, diagnosed according to the requirements of the ACR (radiographs, symptoms and signs) and suffering pain and discomfort in the affected knee most days during the last 3 months. - 80 patients received an i.a. injection of sodium hyaluronate at 2% + mannitol at 0.5% (Ostenil Plus®) during their first visit and were monitored	II-3	A total of 80 patients (aged 40 years or older) diagnosed with class III knee osteoarthritis according to the American College of Rheumatology (ACR) criteria were included in the study.	Osteonil Plus (IAHA + Mannitol)		6 months	**Results:** -Significant reduction in joint pain, stiffness and functional disability compared with baseline was observed at every follow-up visit ($P < 0.001$). - Joint function improved by 38.7% on Day 30, reaching 47.5% on Day 180. -Rescue medication use decreased from 58.2% at baseline to 2.5% on Day 90, increasing in the last visits. -Efficacy and safety were positively evaluated by investigators and patients. -No serious adverse events were observed. -Mild side effects were reported in 4 patients (local pain and swelling in the infiltration area). **Conclusion:** There is evidence that repeated intra-articular injections of HA improve symptoms in KOA. However, studies with a single injection of HA have shown mixed results. This study demonstrates that one single intra-articular injection of non-cross-linked HA reduces joint pain and increases function in patients with KOA over a period of at least 6 months.	Spain

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