INFORMATION BRIEF (RAPID REVIEW)

LORAZEPAM FOR TREATMENT OF SEIZURES IN CHILDREN

Malaysian Health Technology Assessment Section (MaHTAS)
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TITLE: LORAZEPAM FOR TREATMENT OF SEIZURES IN CHILDREN

PURPOSE

To provide brief information on the efficacy/effectiveness, safety and cost-effectiveness of Injection Lorazepam for treatment of seizures following a request from a consultant paediatrician from Hospital Tunku Azizah, Kuala Lumpur.

BACKGROUND

Seizure is a sudden, uncontrolled electrical disturbance in the brain which may lead to changes in behaviour, movements or feeling. It may also affect levels of consciousness. Two or more seizures and recurrent seizures are called epilepsy.[1-3] There are many types of seizures, which ranged in severity. Seizure types vary by where and how they begin in the brain. Most seizures last from 30 seconds to two minutes. A seizure that lasts longer than five minutes is a medical emergency. It could happen after stroke, closed head injury, infections such as meningitis and another illness. The cause of seizure is still unknown.[1-3]

Most seizure disorders can be controlled with medication, but management of seizures can still have a significant impact on the daily life. It is good management to balance seizure control and medication side effects.[1-3]

Benzodiazepines such as diazepam, midazolam and lorazepam reduce seizures occurrence. These drugs may be administered in a number of ways, including into a vein (intravenous), into the mouth (oral) and between the cheeks (buccal), into the nostrils (intranasal) or into the rectum (rectal). The first-choice drug should be effective, work rapidly and not be associated with any serious adverse effects. Research is important to try and find the most effective, the safest anticonvulsant drug and best dosage form to be used in this clinical situation.[1-3]

EVIDENCE SUMMARY

A total of 199 titles were retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from general search engines [Google Scholar and US Food and Drug Administration (USFDA)], using the search term; *seizures, clonic seizure, convulsive seizure, epileptic seizure, complex partial seizure, convulsion, epilepsy, lorazepam, diazepam, midazolam.* Last search was conducted on 14 June 2022. Ten articles were found to be relevant and included in this review which comprised of Systematic Review (SR) and Randomised Controlled Trials (RCTs).

EFFICACY/ EFFECTIVENESS

A recent systematic review conducted by Chhabra R et al. (2021) assessed the efficacy, safety and acceptability of intranasal midazolam in children with acute seizure when compared to IV or rectal diazepam and IV lorazepam. From 10 RCTs included, intranasal midazolam had shorter interval between hospital arrival and seizure cessation with mean difference (MD) -3.51 (95% CI -6.84 to -0.18, p=0.04). However, there were no significant differences with regard to seizure cessation after midazolam or other IV or rectal diazepam/lorazepam administration (MD -0.03, 95% CI -1.30 to 1.25, p=0.97) and in controlling acute seizures between these groups (odds ratio 1.06, 95% CI 0.43 to 2.63, n=737).[4]

A systematic review conducted by McTague A et al. in 2018 (18 RCTs) evaluated drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. The studies vary by design, setting and population, both in terms of their ages and also in their clinical situation. Buccal and intranasal anticonvulsants were shown to lead to similar rates of seizure cessation as intravenous (IV) anticonvulsants, e.g. intranasal lorazepam appears to be as effective as IV lorazepam (risk ratio (RR) 0.96, 95% CI 0.82 to 1.13; 141 children) and intranasal midazolam was equivalent to IV diazepam (RR 0.98, 95% CI 0.91 to 1.06; 122 children).[5]

Another systematic review in 2014 that included 18 studies with a total of 2775 participants evaluated anticonvulsant therapy for status epilepticus.[6] Ten out of 18 studies involved adults, six studies involved children and another two studies included both adults and children. Intravenous lorazepam had statistically significant lower risk of non-cessation of seizures (RR 0.64, 95% CI: 0.45 to 0.90) and of continuation of status epilepticus requiring a different drug or general anaesthesia (RR 0.63, 95% CI 0.45 to 0.88) when compared with IV diazepam. There was no statistically significant different in reducing requirement for ventilator support (RR 0.73, 95% CI 0.36 to 1.49) and adverse effects (risk deficiency (RD) -0.03, 95% CI -0.10 to 0.03). There was a single prospective observational study that included which involved 27 participants reported a statistically non-significant trend favouring IV midazolam regarding the following outcomes: non-cessation of seizures (RR 0.20, 95% CI 0.03 to 1.56); requirement for ventilator support (RR 0.40, 95% CI 0.04 to 3.90) and adverse effects (RR 0.40, 95% CI 0.04 to 3.90) and continuation of status epilepticus requiring a different drug or general anaesthesia (RR 0.20, 95% CI 0.03 to 1.56) when compared with IV lorazepam. The results were summarised as follows:

-Diazepam was better than placebo for cessation of seizures: there was a lower risk of requirement for ventilator support and continuation of status epilepticus requiring a different drug or general anaesthesia with diazepam.

-Lorazepam was better than placebo for cessation of seizures and carried a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia.

-Lorazepam was better than diazepam for cessation of seizures and had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia.
-Lorazepam was better than phenytoin for cessation of seizures.
-For pre hospital treatment, IM midazolam was as effective as and probably better than IV lorazepam for cessation of seizures, frequency of hospitalisation and ICU admissions but not for risk of recurrence of seizures.

Malu et al. (2014) conducted an RCT in Sub-Saharan Africa evaluated the efficacy of sublingual lorazepam versus intrarectal diazepam for prolonged convulsions.[7] A randomized controlled trial was conducted in the paediatric emergency departments of nine hospitals. A total of 436 children aged 5 months to 10 years with convulsions persisting for more than 5 minutes were assigned to receive intrarectal diazepam (0.5 mg/kg, n=202) or sublingual lorazepam (0.1 mg/kg, n=234). Sublingual lorazepam stopped seizures within 10 minutes of administration in 56% of children compared with intrarectal diazepam in 79% ($P < .001$). The probability of treatment failure is higher in case of sublingual lorazepam use (OR: 2.95, 95% CI: 1.91, 4.55). Sublingual lorazepam is less efficacious in stopping paediatric seizures than intrarectal diazepam, and intrarectal diazepam should thus be preferred as a first-line medication in this setting.[7]

Silbergleit et al. (2014) conducted an RCT to evaluate the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of status epilepticus by paramedics.[8] Seizures were absent without rescue therapy at ED arrival in 329 of 448 (73.4%) subjects allocated to active IM treatment and in 282 of 445 (63.4%) allocated to active IV treatment. Among the 119 subjects in the IM group and the 163 in the IV group that failed the primary outcome, 47 (39.5%) and 57 (35.0%) respectively received rescue medications and were not seizing on arrival, and 22 (18.5%) and 42 (25.8%) received rescue medications and were still seizing on arrival. In IM and IV treatment groups, the frequency of endotracheal intubation (14.1% v. 14.4%), recurrent seizures (11.4% v. 10.6%), and other predefined safety outcomes were similar by group. In those admitted, the ICU and hospital length of stay did not vary with treatment group, but the proportion of subjects admitted was significantly lower in the IM group (57.6%) as compared to the IV group (65.6%, p=0.01). Time to administration of drug by the IM route was significantly shorter than by the IV route, but the onset of action (seizure termination) after IV administration was shorter than after IM administration. The overall interval until seizure termination was similar in both groups.[8]

Gathwala et al. (2012) conducted an RCT to evaluate the safety and efficacy of three benzodiazepine drugs: Lorazepam, Midazolam and Diazepam, when given parenterally in the control of acute seizure among children.[9] The patients were randomised to three equal groups of 40 patients each; Group A received diazepam, Group B received midazolam and Group C received lorazepam. The study found that mean duration to clinical seizure cessation was comparable among the three groups; diazepam group (84.94±38.56s), midazolam group (92.69± 25.97s), lorazepam group (91.12±23.58s). Number of patients with any abnormality in seizure cessation were significantly higher in diazepam group [11/40

(27.5%)] when compared to the midazolam [4/40 (10%)] and lorazepam group [2/40 (5%)]. Number of patients requiring second dose to control seizures was significantly higher in diazepam group [4/40, (10%)] when compared to lorazepam group [0/40, (0%)].[9]

SAFETY

The adverse effects (AEs) of all the three parenteral drugs (diazepam, midazolam, lorazepam) among children were comparable in terms of side effects except excessive somnolence which was significantly higher in diazepam group.[9]

COST/COST-EFFECTIVENESS (If any)

Only one retrospective case note audit study conducted by Cock et al. in 2002 that compared cost of lorazepam with diazepam as first-line treatment of convulsive status-epilepticus (CSE) in adult was retrieved.[10] They found that there were no differences reported in adverse effects and drug cost, hence they suggested to use IV lorazepam in preference to IV diazepam as first line treatment for CSE.[10]

CONCLUSION

Based on the review, IV lorazepam significantly lower the risk of non-cessation of seizures when compared with IV diazepam. However, for pre-hospital treatment, intranasal and IM Midazolam showed shorter interval between hospital arrival and seizure cessation as compared to IV lorazepam or diazepam. Intranasal lorazepam had equal rates of seizure cessation with IV lorazepam but sublingual lorazepam was less efficacious in stopping children seizures than intrarectal diazepam. There was higher abnormality in seizure cessation for patients treated with diazepam. The cost of Lorazepam tablet ranged from RM0.50/tablet to RM0.85/tablet (0.5mg-2mg).[11] IV lorazepam was not listed in MOH Drug Formulary and the price was not available in the consumer guide price.[11]

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