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CASE REPORT

Intravenous magnesium sulphate for treatment of pediatric migraine: case series

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Abstract

Magnesium therapy may reduce migraine in children by reducing cortical spread depression and activation of the trigeminovascular complex. It is being used increasingly in Emergency Departments for migraine so we report a case series of children with migraine treated with intravenous (IV) magnesium sulphate. Electronic records were used to identify cases of migraine at our institution from May 2012 to September 2013. Patient records were reviewed to identify those with accurate migraine diagnoses and treatment with IV magnesium sulphate. 18 encounters were identified regarding 9 children. There was a good clinical response in 16 of these encounters and an average time to response of 2.3 hours. Discharge from the Emergency Department (ED) occurred in 10 of the 12 encounters where patients were administered IV magnesium sulphate in ED. Why should an Emergency Physician be aware of this? When oral non-steroidal anti-inflammatories and triptans aren't successful for Emergency presentations of migraine there are a range of therapeutic options with limited evidence. Some of those options have well known risks, for example extra-pyramidal side effects with prochlorperazine and excessive sedation with propofol. Intravenous magnesium sulphate has a good safety profile, minimal side effects and is familiar to most medical and nursing staff. It is a good option as the infusion is brief and the clinical response is timely.

Keywords

Migraine; Pediatric; Intravenous; Magnesium; Emergency

1. Introduction

Childhood migraine has been reported all over the world and prevalence ranges from 1.2–23% [1–11]. The mean onset for migraine is 7 years for boys and 11 years for girls. The incidence of migraine with aura peaks earlier than the incidence of migraine without aura [1, 12–17]. Early treatment measures are important to control and break the attack to allow the child to quickly return to his normal functioning. Evidence for acute management of pediatric migraine is limited. A recent American Academy of Pediatrics (AAP) guideline supports ibuprofen, naproxen and triptans for initial treatment of migraine [18].

There is limited evidence to support the novel use of standard medications such as propofol, prochlorperazine and magnesium to abort migraine after first line treatments have failed [12, 19–25]. This case series and discussion explores the administration of intravenous magnesium sulphate.

2. Method

We conducted a retrospective review of medical records looking at all patients who presented with headache to the Pediatric Emergency Department at the Women's & Children's Hospital in Adelaide, Australia. Electronic database of all patients aged between 5 to 18 years who presented to the ED with Headache were reviewed from May 2012 to September 2013. Medical records for each presentation were assessed for migraine headache diagnosis (defined according to criteria in Tables 1 and 2) and intravenous (IV) magnesium sulphate treatment. Data on sex, age, Migraine classification regarding aura, pain score on presentation and pain score following IV magnesium sulphate treatment, time to improvement if present, side effects, treatment in ED or as an inpatient, and final outcome were collected. Patients who were unstable or with underlying conditions or etiology for headaches were excluded. Clinical improvement with treatment was considered to be a reduction in pain score of >2.

2.1 Case series

128 patient records were reviewed. Patients with a non-migrainous etiology for their headache (n = 2) and those who did not receive IV magnesium treatment (n = 107) were excluded. One case was excluded as documentation of magnesium administration was incomplete. 18 presentations were

TABLE 1. Criteria for migraine headaches with aura [26].

Diagnostic criteria for Migraine with Aura (International Classification of Headache Disorders (ICHD-3) beta):
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
• 1. Visual
• 2. Sensory
• 3. Speech and/or language
• 4. Motor
• 5. Brainstem
• 6. Retinal
C. At least two of the following four characteristics:
• 1. At least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
• 2. Each individual aura symptom lasts 5–60 min
• 3. At least one aura symptom is unilateral
• 4. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis, transient ischaemic attack has been excluded

TABLE 2. Criteria for migraine headaches without aura [26].

Diagnostic criteria for Migraine without Aura (International Classification of Headache Disorders (ICHD-3) beta):
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
• 1. Unilateral location
• 2. Pulsating quality
• 3. Moderate or severe pain intensity
• 4. Aggravation by or causing avoidance of routine physical activity (*e.g.*, Walking or climbing stairs)
D. During headache at least one of the following:
• 1. Nausea and/or vomiting
• 2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

suitable for inclusion. This represented 9 patients, some of whom had multiple presentations (See Table 3).

There were 5 males and 4 females and the average age was 15 years. 9 out of 18 encounters were migraine with aura. All patients had received treatment with prior medications (Paracetamol, ibuprofen, aspirin, promethazine, morphine, sumatriptan, topiramate, oxycodone, fentanyl patch, tramadol) prior to treatment with IV Magnesium. The dose of magnesium sulphate IV was 0.1 mmol/kg by slow infusion (30–60 minutes) in all cases except one where 0.15 mmol/kg was administered. On 16 of the patient encounters there was clinical improvement. The average time to clinical improvement was 2.3 hours and the average duration of stay in the ED was 7.3 hours.

On 12 patient encounters the patient received IV magnesium in Emergency and on 10 of those occasions they were discharged home. On 6 occasions the patient received IV magnesium only after being transferred to the wards.

Regarding side effects only 2 patients reported IV site pain, burning or discomfort but the infusions were still completed. No patients had worsening of headache following IV magnesium.

TABLE 3. Summary of patients for whom intravenous magnesium sulphate was administered. Where individuals had more than 1 presentation, data from the 1st presentation is shown.

Patient	1	2*	3	4	5	6**	7	8***	9
Age	17	17	16	13	17	7	11	17	11
Sex	F	M	M	F	M	F	F	M	M
Aura	Visual Hallucination, Photophobia	Nil	Photophobia	Photophobia, blurred vision	Facial numbness	Photophobia	Hemiplegia	Photophobia, Left ptosis	Photophobia, Left ptosis
Pre $MgSO_4$ pain score	7–8	7	7	6	7	7	7	6	4
Post $MgSO_4$ pain score	2–3	4	5	3	0	0	1	3	0
Side Effects	Nil	Hypotension	IV site pain	IV site pain	Nil	Nil	Nil	Nil	IV site pain
Time to improvement (min)	20	95	35	120	115	75	<24 h	15	210
Mg given in ED/Inpatient	Pediatric Ward	ED	ED	ED	ED Short Stay	Neurosurgery Ward	Pediatric Ward	ED	Pediatric Ward
Final Outcome (time to discharge post $MgSO_4$)	Admitted Inpatient	9 h	3 h 10 m	6 h 30 m	6 h 40 m	Admitted inpatient	Admitted inpatient	3 h 30 m	Admitted inpatient

**Patient had 5 separate presentations; **Had 3 separate presentations; ***Had 4 separate presentations. F: Female; M: Male; IV: intravenous; ED: Emergency Department; $MgSO_4$: Magnesium Sulphate.*

2.2 Case example

Patient 2 was a 17 years old male with frequent migraines for one month, on the background of 2 years of migraine. He had previously been trialed on sumatriptan, propranolol, Non-steroidal anti-inflammatory drugs (NSAIDS) and fentanyl patches. There was family history of migraine in his sister and maternal aunt. He was a grade A student at school.

On one presentation to the ED, he had history of right-sided migraine headache for 3 days which had commenced during school. There was a history of associated dizziness but no aura. He had taken ibuprofen, aspirin, paracetamol and sumatriptan over the days with only some temporary initial improvement.

On examination his pain score was 7/10, he was alert, with normal vital signs, normal neurological and systematic examination. After assessment he was treated with magnesium sulphate infusion (0.1 mmol/kg). His pain score settled to 4/10 following the infusion and he was discharged 5 hours after treatment.

This patient had 5 separate presentations to our ED with Migraine. He was administered intravenous magnesium sulphate each time. He demonstrated a good response on 3 of the 5 occasions with no side effects.

3. Discussion

A current theory based on the Trigeminovascular complex (TVC), describes the hyper-excitable trigeminoneurovascular neurons that release neurotransmitters such as Calcitonin Gene Related Peptide, causing vasodilatation, mast cell degranulation, increased vascular permeability and ultimately meningeal inflammation [27–29]. The nociceptive data is relayed along the trigeminal nerve to the trigeminal nucleus caudalis, thalamic nuclei and cortex where the migraine pain is finally expressed [27, 28]. Regarding the aura, it is thought to be related to cortical spreading depression (CSD). CSD is the excitation followed by prolonged spreading depolarization of the cortex, which is associated with oligaemia. N-Methyl-D-Aspartate receptor stimulation and Calcitonin-related Peptide released by the activated TVC are both vasodilators and play a role in pain transmission [27, 29]. They are both antagonized by magnesium. Regarding cerebrovascular constriction, which can be induced by serotonin, magnesium is once again antagonistic [27, 29].

Several studies have confirmed an association between migraine attacks and low magnesium levels in serum, cerebrospinal fluid and in saliva [27, 29]. Mauskop A. *et al.* [30] published a review of several studies looking at magnesium levels in patients diagnosed with migraine headaches, and concluded that up to 50% of patients with migraine headaches will also have magnesium deficiency. In 2016 Hsiao-Yean Chiu *et al.* [31] published a meta-analysis of randomized controlled trials in adults that evaluated intravenous and oral magnesium in acute migraine that demonstrated significant improvements.

Some studies however showed no improvement with the use of magnesium for migraine headaches. Hyun Choi showed no benefit to the use of magnesium in a meta-analysis review of randomized controlled studies [32]. However, in this study it is important to note that he evaluated the effect of magnesium at 30 minutes after administration. It is possible that magnesium may have shown a positive effect at 1 or 2 hours after administration (See Table 4) [32].

In pediatrics Wang *et al.* [33] assessed oral magnesium as a prophylactic treatment and found a trend towards reduced migraine frequency. Gertsch *et al.* [34] published a case series in this journal of 20 children who received intravenous magnesium for headache and 7 of those children had a favorable response.

In our study, Intravenous Magnesium therapy was an effective abortive treatment for patients presenting to our Pediatric Emergency Department. Although IV magnesium is widely used in various childhood illnesses, there is limited reported evidence for its use as an abortive therapy for migraine headaches in the pediatric population. Clinician experience in using IV magnesium sulphate in pediatric emergency as well as its history of safe use make it a good alternative for abortive therapy once first line therapies have failed.

There are several limitations in our case series, particularly as it is a retrospective casenote review so the documenting clinicians are not blinded and may be biased. Patient assessments were not standardized. Some patient data was incomplete and the patient sample size was small.

Despite these limitations it is helpful to document more children who have received intravenous magnesium sulphate without complication. As described in the introduction there are several plausible mechanisms of action. Its use as an abortive therapy for pediatric migraine is promising and further randomized, double-blind controlled studies should be conducted.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

DSG, PTW and HG—designed the research study. HG, PTW—performed the research. HG, PTW and DSG—analyzed the data. HG and DSG—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee at the Women's and Children's Hospital, Adelaide (Study Reference Number: 656A). All subject's consent was obtained in accordance with guidelines of the WCHN Human Research and ethics committee.

TABLE 4. List of randomized controlled trial studies in patients with migraine attacks treated by intravenous magnesium.

Author, Year	Country	Setting	Intervention	Control	Measures	Observation time point after infusion
Bigal, [31] 2002	U.S.A.	2 Public Health Units	1 g Magnesium sulphate	0.9% Saline 10 mL	Response rate	30 and 60 min, 24 h
Cete, [31] 2005a	Turkey	ED	2 g Magnesium sulphate	10 mg Metoclopramide	VAS	15 and 30 min
Cete, [31] 2005b	Turkey	ED	2 g Magnesium sulphate	0.9% Saline	VAS	15 and 30 min
Corbo, [31] 2001	U.S.A.	2 Urban ED	2 g Magnesium citrate + 20 mg Metoclopramide	20 mg Metoclopramide + 0.9% Saline	VAS	45 min
Demirkaya, [31] 2001	Turkey	Headache Clinic	1 g Magnesium sulphate	0.9% Saline 10 mL	Response rate	30 min
Li, [31] 2013	China	UK	32 mg Magnesium chloride Adenosine Disodium Triphosphate + 80 mg Ozagrel	Regular analgesic and anti-emetic use	Response rate	24 h
Liu, [31] 2013	China	UK	32 mg Magnesium chloride Adenosine Disodium Triphosphate + 80 mg Ozagrel	Regular analgesic and anti-emetic use	Response rate	120 min
Shahrami, [31] 2015	Iran	ED	1 g Magnesium sulphate	8 mg dexamethasone +10 mg metoclopramide	Response rate	20, 60, and 120 min

TABLE 4. Continued.

Author, Year	Country	Setting	Intervention	Control	Measures	Observation time point after infusion
Tang, [31] 2011	China	UK	32 mg Magnesium chloride Adenosine Disodium Triphosphate + 80 mg Ozagrel	Regular analgesic and anti-emetic use	Response rate	120 min
Wang, [31] 2010a	China	UK	40 mL Magnesium Aspartate and Potassium Aspartate	Ergotamine	Response rate	24 h
Wang, [31] 2010b	China	UK	40 mL Magnesium Aspartate and Potassium Aspartate	2 g Vit C + 5% glucose 500 mL	Response rate	24 h
Wang, [31] 2013	China	UK	32 mg Magnesium chloride Adenosine Disodium Triphosphate + 80 mg Ozagrel	Regular analgesic and anti-emetic use	Response rate	120 min
Xu, [31] 2010	China	UK	25% magnesium sulphate 15 mL + 20% lidocaine 0.5 mL in canula	Aspirin and Tiapride	VAS	60, 120, 180 min

ED: Emergency Department; VAS: Visual Analogue scale; UK: Unknown.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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