Clinical Neurology and Neurosurgery 178 (2019) 31–35

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Experiences of an outpatient infusion center with intravenous magnesium therapy for status migrainosus

Fanny Xu[a,*], Anush Arakelyan[b], Andrew Spitzberg[a], Lauren Green[c], Paul-Henri Cesar[c], Anne Csere[c], Olive Nworie[c], Soma Sahai-Srivastava[c]

[a] USC Keck School of Medicine, Los Angeles, USA
[b] Department of Neurological Surgery, USC Keck School of Medicine, Los Angeles, USA
[c] Department of Neurology, USC Keck School of Medicine, Los Angeles, USA

ARTICLE INFO

Keywords:
Magnesium
Migraine
Headache
Pain
PGIC
Observational
Retrospective

ABSTRACT

Objectives: Exploratory study to investigate the effectiveness of intravenous magnesium as an abortive for status migrainosus in an outpatient infusion center, and characterize the patients who benefit from the therapy.
Patients & methods: Retrospective analysis of 234 migraine patients who received IV magnesium as a headache abortive, at the headache clinic of University of Southern California. Additional intramuscular (IM) injections for nausea (prochlorperazine, odansetron, metoclopramide) or for refractory pain (ketorolac, dexamethasone, sumatriptan, dihydroergotamine), were administered as necessary. Immediately before and after treatment, self-reported pain levels were recorded using an 11-point numeric pain rating scale (0–10).
Results: Our patient sample has a mean age of 44 years and was predominantly female (79%). 36 (19%) had migraine with aura. Overall, pain score decreased from 5.46 ± 2.39 to 3.56 ± 2.75 ($P < 0.001$) after magnesium infusion. One hundred twenty-seven (54%) patients had clinically significant pain reduction, as defined by pain decrease ≥ 30%. One hundred and four patients (44%) received IV magnesium and did not require additional intramuscular (IM) medications for pain. In patients who did not receive additional IM medications for pain, pain score decreased from 4.76 ± 2.41 to 2.95 ± 2.70 ($p < 0.001$), and 61 out of 104 (59%) experienced ≥ 30% pain reduction. Patients with less severe pain tended to have a better response than patients with more severe pain, as patients with ≥30% pain reduction had a significantly lower pre-treatment pain score ($p = 0.018$).
Conclusion: For a subset of patients with status migrainosus, IV magnesium therapy results in clinically significant pain relief without the need for intramuscular pain medications. Therefore, IV magnesium may be useful as a cost-effective first-line parental therapy for status migrainosus, especially for patients who initially present with lower pain intensity.

1. Introduction

Over the past decades, there has been a revived interest in magnesium as a therapeutic option for migraine headache. The link between magnesium and migraines is not completely novel, as there have been a few isolated case studies of magnesium relieving migraine headaches as far back as the 1930s [1,2]. In 1973, a German-language article published by Vosgerau was the first case study series that noted successful resolution of migraine headaches in 10 patients [2,3]. However, it was not until the late 1980s did researchers draw a definitive connection between migraines and magnesium imbalance. Using in-vivo ^{31}P NMR spectroscopy, Ramadan et al. demonstrated that patients had transiently decreased levels of intracellular magnesium in the brain cortex during a migraine attack [4]. Other studies with migraine patients demonstrated decreased magnesium in serum, RBC, and CSF [2,5–8]. As a result, there has been renewed enthusiasm in the role of magnesium in migraine pathophysiology and its potential as a treatment option.

Today, we still lack a complete understanding of magnesium in migraine pathophysiology. Generally speaking, magnesium is involved in many cellular processes including acting as a cofactor for more than 300 enzymes [9]. Magnesium imbalance is known to have clinical manifestations including abnormal neuromuscular excitability, cardiac

Abbreviations: Mg, magnesium; IV, intravenous; IM, intramuscular; PGIC, Patient's Global Impression of Change scale; SD, standard deviation; CIs, 95% Confidence Intervals; N, number

* Corresponding author.
E-mail addresses: fanxu91@gmail.com (F. Xu), sahai@med.usc.edu (S. Sahai-Srivastava).

https://doi.org/10.1016/j.clineuro.2019.01.007
Received 3 December 2017; Accepted 15 January 2019
Available online 21 January 2019
0303-8467/

conduction, and disruption of calcium metabolism [10]. In migraine pathogenesis, many possibilities regarding magnesium's role have been postulated to explain the transient hypomagnesemia has been associated with migraine events. Magnesium has been shown to regulate NMDA glutamate receptors, which are involved in pain transmission and cortical spreading depression, and therefore may suppress migraine aura. Furthermore, magnesium levels have been shown to affect levels of calcitonin gene-related peptide (CGRP) and nitrous oxide (NO), both of which have known associations with migraine headache [11].

Due to potential for benefit and a low risk profile, clinicians have made extensive use of oral magnesium as prophylaxis for migraine headache. Guidelines from the American Headache Society (AHS) and American Academy of Neurology (AAN) list oral magnesium as a Level B recommendation for prevention of episodic migraine [12]. Increasing dietary intake of magnesium-rich foods has also been suggested as an alternative to magnesium supplementation [13].

More recently, intravenous (IV) magnesium has been explored as a potential abortive for migraine headache. Due to its low risk profile and potential benefits, Mauskop & Varughese suggested that IV magnesium should be the first parenteral option for all patients with status migrainosus [14]. However, information regarding its effectiveness remains limited and inconclusive. Of the few randomized controlled trials (RCT) that are available, some have supported the effectiveness of IV magnesium [15–18], while others found no benefit [19–21].

In our study, we sought to determine the effectiveness of IV magnesium in the setting of an outpatient headache infusion center, and attempted to characterize patients who are more likely to benefit from the intervention. With 234 patients in our retrospective analysis, this is the largest observational study to date concerning the use of intravenous magnesium in status migrainosus.

2. Materials & methods

2.1. Study design and setting

This study is a retrospective chart review conducted at our headache clinic at the University of Southern California. In addition to providing consultations from neurologists trained in pain medicine, our specialty clinic houses an infusion center to administer headache abortives and prophylaxis. Since 2014, IV magnesium has been included as an elective treatment for patients seeking migraine relief. For these patients, IV magnesium sulfate (2 g diluted with 50–100 cc of normal saline) is administered over 1–2 h. Additional intramuscular (IM) injections for nausea (prochlorperazine, odansetron, metoclopramide) or for refractory pain (ketorolac, dexamethasone, sumatriptan, dihydroergotamine) are administered as necessary. This study was approved by the University of Southern California institutional review board.

2.2. Clinical chart review

The retrospective chart review includes visits from 234 patients who met criteria set by the International Classification of Headache Disorders (ICHD-3 beta) [22] for status migrainosus and received IV magnesium therapy from February 2014-September 2016. In the recorded visits, the patient was seeking a headache abortive at the time of presentation. This analysis excludes visits in which patients had no pain at presentation and received IV magnesium exclusively for migraine prophylaxis. We also excluded visits without pain scores recorded, as well as repeat visits by patients who received multiple magnesium infusions.

Demographic data collection included age, gender, ethnicity, and diagnosis. A subset of patients chose to respond to a clinical questionnaire, which provided additional data including presence of an aura and other descriptors of headache. Any IM medications used during the visit were also recorded.

Benefit from IV magnesium therapy was mainly assessed using self-reported pain scores available on patient charts. An 11-point numeric pain scale (0–10) was used by the patient to rate pain immediately before and after infusion. Some patients also provided a rating of their overall impression of treatment efficacy with the Patients' Global Impression of Change (PGIC) scale (1–7) after magnesium infusion. The PGIC allows the patient to indicate whether treatment resulted in as no significant change (scored 1–4) or significant favorable change (scored 5–7) [23].

In order to assess whether pain reduction is clinically meaningful, we set thresholds of 30% and 50% pain decreases. This is based on previous studies showing that with an 11-point (0–10) pain intensity scale, a reduction of 30% correlates with patient reports of "much improved," and a 50% reduction correlates with "very much improved" on the PGIC scale [24,25]. This was used as a more consistent measure of clinical significance as not all patients were administered the PGIC questionnaire.

2.3. Statistical analysis

Descriptive statistics and univariate analyses were generated and are presented in the results section. Mean, Standard Deviation (SD), Minimum (Min), Maximum (Max), and 95% confidence intervals (CI) are summarized in Tables 1–3 as part of descriptive statistics. P-values included in tables are generated from univariate statistical tests. Non-parametric (Wilcoxon-Mann-Whitney or Wilcoxon Signed-Rank) tests or two-sample t-tests were performed as appropriate depending on the variable distribution and the analysis type (matched/unmatched). For all tests, two-tailed P values were calculated and P-values < 0.05 were considered to be significant. All analyses were performed using the statistical software package Stata/IC (version 14.2, StataCorp, LP).

3. Results

3.1. Demographics

Our patient sample of 234 migraine patients had an age range of

Table 1
Demographics and pre-treatment pain scores. Patient numbers, demographic features, presence of aura, and whether intramuscular (IM) pain medications (ketorolac, dexamethasone, sumatriptan, dihydroergotamine) were administered in addition to IV magnesium. Age and self-reported pain scores on presentation (0–10) were compared between groups.

			95% CI			
	Mean	SD	Lower	Upper	P-Value	N
Age	44	16	42	46		234
Male	40	15	36	45	0.078	48
Female	45	15	43	47		186
Non-Hispanic White	43	16	40	46	0.194	134
Hispanic	46	15	41	51		39
African American	53	11	45	61		10
Asian	46	12	36	56		8
Other Ethnicity	42	15	37	47		43
Migraine with Aura	38	12	34	42	**0.037**	36
Migraine without Aura	45	16	42	47		158
Pre-Treatment Pain Score	5.46	2.39	5.15	5.77		234
Male	4.83	2.34	4.15	5.51	**0.030**	48
Female	5.62	2.39	5.27	5.96		186
Non-Hispanic White	5.37	2.40	4.95	5.78	0.211	134
Hispanic	6.00	2.33	5.25	6.75		39
African American	6.70	2.87	4.65	8.75		10
Asian	4.88	2.10	3.12	6.63		8
Other Ethnicity	5.07	2.27	4.37	5.77		43
+ Pain IM Meds	6.02	2.23	5.63	6.40	$<$ **0.001**	130
- Pain IM Meds	4.76	2.41	4.29	5.23		104
Migraine with Aura	5.64	2.53	4.78	6.50	0.762	36
Migraine without Aura	5.51	2.38	5.14	5.89		158

Table 2
Outcomes after magnesium infusion (all). Outcome measures include self-reported post-treatment pain score (0–10), which was compared with pre-treatment pain score in Table 1. Percent change was calculated, with a negative number indicating a reduction in pain score, and compared between patients with and without aura / rescue intramuscular (IM) medication use. Patient Global Impression of Change (PGIC) score [1–7] was compared between groups when data was available.

			95% CI			
	Mean	SD	Lower	Upper	P-Value	N
Post-Treatment Pain Score*	3.56	2.75	3.21	3.91	**0.000**	234
Migraine with Aura	3.83	2.61	2.95	4.72	0.607	36
Migraine without Aura	3.66	2.82	3.22	4.10		158
+ Pain IM Meds	4.05	2.70	3.58	4.51	**0.001**	130
- Pain IM Meds	2.95	2.70	2.43	3.48		104
Percent Change in Pain Score	−0.38	0.43	−0.44	−0.33		234
Migraine with Aura	−0.37	0.33	−0.49	−0.26	0.872	36
Migraine without Aura	−0.37	0.44	−0.44	−0.30		158
+ Pain IM Meds	−0.33	0.41	−0.40	−0.26	0.067	130
- Pain IM Meds	−0.44	0.44	−0.53	−0.36		104
Pre-Treatment Pain Score						
Pain Decrease of ≥30%	4.98	2.34	4.57	5.39	**0.001**	127
Pain Decrease of < 30%	6.02	2.35	5.57	6.47		107
Pain Decrease of ≥50%	4.73	2.32	4.27	5.19	**< 0.001**	99
Pain Decrease of < 50%	5.99	2.31	5.60	6.39		135
PGIC	3.74	1.90	3.44	4.05		149
Pain Decrease of ≥30%	4.37	1.68	4.00	4.74	**< 0.001**	81
Pain Decrease of < 30%	3.00	1.89	2.54	3.46		68
Pain Decrease of ≥50%	4.67	1.59	4.26	5.08	**< 0.001**	60
Pain Decrease of < 50%	3.12	1.85	2.73	3.51		89

Table 3
Outcomes for patients who received IV magnesium only. Outcome measures were separately analyzed in our sample of 104 patients who did not receive intramuscular (IM) pain medication in addition to IV magnesium. These include self-reported post-treatment pain score (0–10), which was compared with pre-treatment pain score in Table 1, percent change in pain score, and Patient Global Impression of Change (PGIC) score [1–7].

			95% CI			
	Mean	SD	Lower	Upper	P-Value	N
Post-Treatment Pain Score	2.95	2.70	2.43	3.48	**< 0.001**	104
Migraine with Aura	3.27	3.01	1.60	4.93	0.869	15
Migraine without Aura	3.06	2.65	2.43	3.68		72
Percent Change in Pain Score	0.44	0.44	−0.53	−0.36		104
Migraine with Aura	−0.44	0.39	−0.65	−0.22	0.896	15
Migraine without Aura	−0.42	0.45	−0.52	−0.31		72
Pre-Treatment Pain Score	4.76	2.41	4.29	5.23		104
Pain Decrease of ≥30%	4.28	2.26	3.70	4.86	**0.018**	61
Pain Decrease of < 30%	5.44	2.48	4.68	6.21		43
Pain Decrease of ≥50%	3.96	2.13	3	5	**0.002**	48
Pain Decrease of < 50%	5.45	2.44	5	6		56
PGIC	4.12	1.83	3.67	4.56		68
Pain Decrease of ≥30%	4.66	1.56	4.17	5.15	**0.003**	41
Pain Decrease of < 30%	3.30	1.94	2.53	4.06		27
Pain Decrease of ≥50%	5.00	1.37	4	6	**< 0.001**	31
Pain Decrease of < 50%	3.38	1.86	3	4		37

15–88 years, and a mean age of 44 years. They were predominantly female (80% female vs 20% male). Fifty-seven percent are identified on medical records as non-Hispanic white, 17% Hispanic/Latino, 26% Other. The largest demographic group studied was non-Hispanic white female (45%). Table 1 lists these demographic variables.

Mean pain score before magnesium infusion was 5.46 ± 2.39. Females were significantly more likely to have a higher pre-intervention pain score, as females had a mean score of 5.62 ± 2.39, compared to males who had a mean score of 4.83 ± 2.34 (p = 0.03). There were no significant differences in pre-treatment pain scores among the categories of race/ethnicity.

Only 36 patients have been recorded as having migraine with aura (15%), in comparison to 158 diagnoses of migraine without aura (67%). The presence of an aura was not specified in 40 patients (17%) and these were considered as missing values when performing analyses. In our sample, patients with aura were significantly younger with a mean age of 38, compared to patients without aura who had a mean age of 45 (p = 0.037).

3.2. Treatment

In our sample of 234 patients, 104 (44%) received only IV magnesium for pain, with 15 of these patients receiving an IM anti-emetic as well (prochlorperazine, odansetron, metoclopramide). Meanwhile, 130 (56%) patients received other methods of pain relief, with IM ketorolac, dexamethasone, sumatriptan, and dihydroergotamine in addition to magnesium infusion. Patients who required IM medications for pain in addition to IV magnesium had a higher pre-intervention pain score (mean = 6.02 ± 2.23) compared to those who only received IV magnesium for pain (mean = 4.76 ± 2.41,p < 0.001).

Overall, there was a decrease in pain score from 5.46 ± 2.39 to 3.56 ± 2.75 (p < 0.001), with a mean percent reduction of 38%. Table 2 describes the overall response to treatment in our sample. Difference in pain score before and after treatment was statistically significant regardless of sex, race/ethnicity, and presence of an aura. Out of 234 patients, 127 patients (54%) experienced pain reduction ≥ 30% and 99 (42%) patients had pain reduction ≥ 50% (Fig. 1a). Percent pain reduction was not significantly affected by sex, age, race/ethnicity, or presence of an aura. However, patients who had a greater pain reduction were more likely to have had presented with a lower initial pain score. Patients who had a percent pain reduction of ≥50% (which correlates with "very much improved" [24]) had an initial pain score of 4.73 ± 2.32, while patients who had a percent pain reduction < 50% had an initial pain score of 5.99 ± 2.31 (p < 0.001). Only 2 patients reported adverse effects, one with transient hypotension and the other with diarrhea.

Patients rated their overall impression of change as 3.74 ± 2.34 on the PGIC scale (“a little better”/”somewhat better”). This does not meet criteria for clinical significance, which requires a score of 5–7 to be considered a significant, favorable change [23]. However, response rate to the PGIC questionnaire was only 64%. For those who responded to the questionnaire PGIC score was correlated with percent pain reduction (Fig. 2).

To remove the confounding variable of administered IM medications, we separately analyzed treatment responses of the 104 patients who only received IV magnesium for pain (Table 3). In these patients, pain score decreased from 4.76 ± 2.41 to 2.95 ± 2.70 (p < 0.001). The difference in pain scores before and after treatment was statistically significant regardless of sex, presence of aura, or ethnicity.

Patients who only received IV magnesium for pain had a mean percent reduction of 44%. Out of 104 patients, 61 patients (59%) experienced pain reduction ≥ 30%, and 48 patients (46%) had pain reduction equal or more than 50% (Fig. 1b). As in the overall sample, pain reduction was also not significantly affected by sex, age, ethnicity, or presence of an aura. Patients who had a percent pain reduction of ≥50% had an initial pain score of 3.96 ± 2.13, compared to 5.45 ± 2.44 in patients with less pain reduction (p = 0.002).

In this group, patients who responded to the PGIC questionnaire (65%) rated their overall impression of change as 4.66 ± 1.56 on the PGIC scale ("somewhat better"). PGIC score was significantly higher in patients who had a percent pain reduction of ≥50%, 5.00 ± 1.37 versus 3.38 ± 1.86, meeting the criteria for clinically significant favorable change.

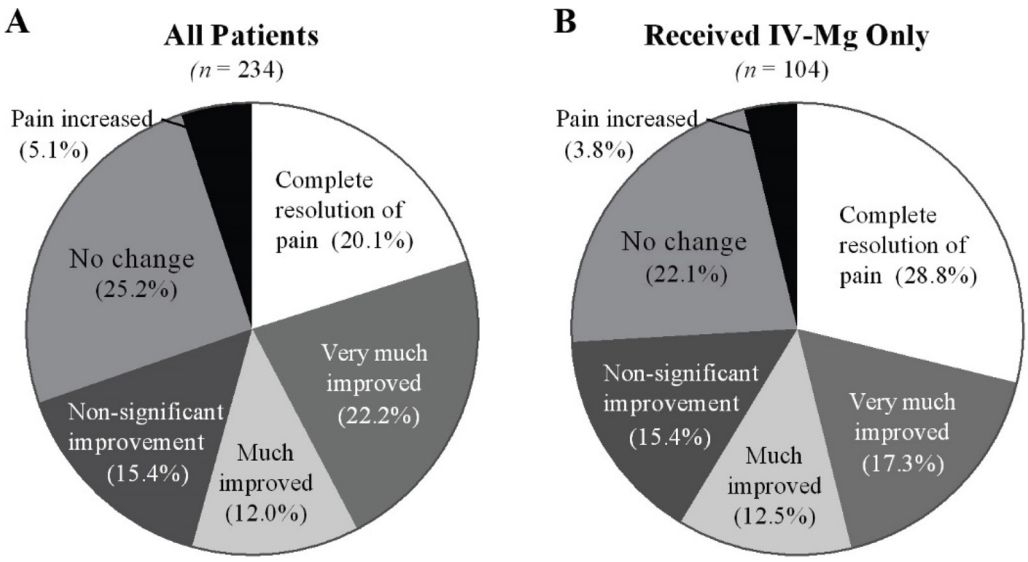

Fig. 1. Change in pain score after IV magnesium. Pie graph categorizing patient change in pain score in overall sample of 234 patients (A) or patients who received only IV magnesium for pain, i.e. no intramuscular (IM) pain medications (B). Categories are defined as follows: no change (0% reduction), improvement not clinically significant (0–29.9% reduction), much improved (30–49.9% reduction), very much improved (50%–99.9% reduction), and complete resolution of pain (100% reduction).

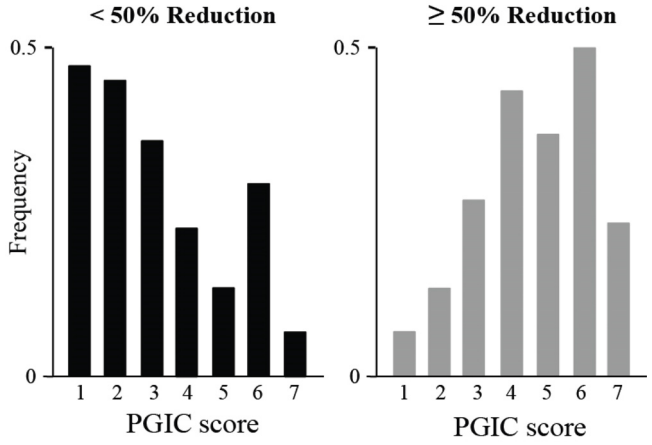

Fig. 2. PGIC score by pain reduction category. Distribution of Patient Global Impression of Change (PGIC) scores [1–7] from the 149 patients who answered the questionnaire, compared between patients who did and did not experience a pain score reduction of ≥ 50%.

4. Discussion

Currently, our retrospective analysis with 234 is the largest observational study evaluating the potential role of intravenous magnesium as a headache abortive in status migrainosus. Out of our total sample, about 40% of patients did not require additional intramuscular pain medications after administration of IV magnesium, over half (59%) of whom experienced a pain reduction of 30% or more. On average, these patients experienced a 44% reduction in pain, with a mean pain difference of about 2 points on a numeric pain scale (0–10).

These findings may support the role of IV magnesium in status migrainosus, which has a pathophysiological basis. Among the various mechanism proposed, magnesium levels have been shown to affect levels of calcitonin gene-related peptide (CGRP) and nitrous oxide (NO), both of which help regulate cerebral blood flow and pain transmission [11]. However, IV magnesium for migraine headache has been more controversial in practice, as a 2014 meta-analysis of 5 randomized controlled trials from 2001 to 2015 (n = 295) failed to demonstrate significant reduction in pain [26]. Another meta-analysis was conducted in 2016 (n = 948), which excluded 2 studies that were in the prior analysis because they included non-migraine headaches, and added 6 studies published in Chinese. This latter meta-analysis did found that IV magnesium significantly relieved acute migraine headaches within an hour after infusion. Of note, most of the Chinese studies used formulations other than magnesium sulfate (i.e. magnesium chloride adenosine disodium triphosphate, magnesium aspartate), and had longer infusion times. As a result of insufficient data, IV magnesium is currently not recommended by the American Headache Society [27].

Our intervention had some procedural differences with the previous studies. We infused 2 g of magnesium sulfate (diluted with 50–100 cc of normal saline) over 1–2 h, while all previous studies published in English had 1–2 g infused over 20 min or less [15–19]. Furthermore, out of the 5 English-language RCTs that only included migraine patients, 3 had observational endpoints at under an hour, with Cete et al. and Corbo et al. finding no beneficial effect with IV magnesium at 30–45 min [18,19,21]. Cete et al. further specified that in their study, the 30-minute endpoint was measured from the beginning of the infusion, since absorption and distribution should occur within minutes with the intravenous route. In contrast, our observational endpoint was assessed at about 1–2 h from the beginning of the infusion.

When compared to RCTs that found a significant benefit for IV magnesium, our results were relatively modest. Among our patients who only received IV magnesium, 29% were completely free of pain after 1–2 h of infusion, similar to Bigal et al. who found that 30% (18/60) were free of pain at 1 h. On the other hand, Demirkaya et al found a pain-free rate of 87% (13/15) at 2 h [16,17]. Furthermore, in our group who received IV magnesium only, the mean percent pain reduction was 44%, while Shahrami et al, found percent changes of 35% at 1 h and 92% at 2 h [15]. These differences may be attributable to our larger sample size as well as our observational endpoints varying between 1–2 h, as the pain scores were obtained in a clinical setting.

In regards to the patients in our study who experienced no change or a slight increase in pain after infusion of IV magnesium, it is important to point out that even for therapies with Level A recommendations, there are always a subset of patients whose headaches remain refractory to treatment. For example, in an RCT with sumatriptan injections, 30% of patients had not experienced headache relief at 2 h [28].

We did find that patients who present with less severe headaches are more likely to experience pain relief with IV magnesium infusion. Patients who required IM pain medications in addition to IV magnesium were significantly more likely to have a higher pre-treatment pain score (6.02 compared to 4.76). Furthermore, within the group who received IV magnesium only, patients who had clinically meaningful pain reduction had a lower mean pre-treatment pain score than those who did not (4.28 compared to 5.44). This suggests that patients are more likely to derive benefit from IV magnesium if they have milder headaches,

while more severe headaches require adjunct medications. Tentative explanations include the possibilities that headache attributable to magnesium imbalance may be less severe than headaches attributable to other causes, less severe headaches may represent early presentations that are more easily treatable than later presentations of status migrainosus, or simply that IV magnesium infusion provides mild and fixed pain relief that is more easily perceived in mild headaches.

We also examined whether the presence of migraine aura affected differences in response. Previously, Bigal et al. had found that IV found significant pain relief for migraines with aura, but not migraines without aura [16]. The difference in response could have been attributed to magnesium regulation of NMDA receptors, a subtype of which has been shown to trigger cortical spreading depression (CSD) in human neocortical tissue and at models [11]. CSD is characterized by a prolonged depolarization that spreads throughout the cortex, and is thought to be the mechanistic explanation for migraine aura. Magnesium has been shown to suppress CSD in rat models, which has been attributed to its ability to bind and inactivate the NMDA receptor [11].

Nevertheless, we did not observe a difference in response between patients with or without aura in our study. However, we must be cautious in interpretation, as the presence of aura has been one of the more difficult data points obtained through chart review. Many patients (17%) did not have information in their charts that specified whether they had an aura, and it is possible that patients could have been miscategorized due inconsistency in how migraine auras were documented.

This exploratory study is subject to a number of limitations. First there are the usual limitations of a retrospective analysis, as some data was not always readily available, including ethnicity, presence of migraine aura, and PGIC score. In regards to adverse effects, only 2 were recorded (transient hypotension and diarrhea) but it is probable that patients did not report mild adverse effects after the clinic visit.

Confounding magnesium deficiency status was a consideration, but serum magnesium and other measures of magnesium status were not routine labs for patients, and were therefore not recorded for patients in this study. It must also be noted that magnesium status is difficult to assess, as less than 2% of magnesium circulate in the serum, while 31% is intracellular and 67% is stored in the bone [11].

Furthermore, without a comparison group, we cannot make definitive statements after effectiveness. Though our findings will be useful in the design of a future prospective study, we cannot definitively state in this retrospective analysis that a similar level of pain reduction would not have appeared without intervention. Finally, the study population lacked sufficient representation among African and Asian Americans, and the predominance of non-Hispanic white females in our sample may limit generalizability to other demographics.

5. Conclusion

For a subset of patients with status migrainosus, intravenous magnesium therapy results in clinically significant pain relief without the use of intramuscular pain medications. Since 26% of patients in our retrospective analysis experienced clinically significant pain relief with IV magnesium alone, it may be reasonable to choose IV magnesium as the first parental option for migraine headache, especially considering its low risk profile and cost-effectiveness. Better response to therapy is observed in patients who present with less severe headaches, while more severe headaches can benefit from a combination of IV magnesium and IM medication such as ketorolac, dexamethasone, sumatriptan, and dihydroergotamine. Our findings will be used to inform the design of a future prospective study with a comparison group, for a more definitive analysis of effectiveness and to better identify patient characteristics that may affect response to therapy.

Conflict of interest statement

None of the listed authors have a conflict of interest.

Sources of financial support

None.

Acknowledgments

None.

References

[1] N. Pines, M.B. Kieff, Magnesium sulphate in the treatment of angiospasm, Lancet 221 (1933) 577–579.
[2] D.R. Swanson, Migraine and magnesium: eleven neglected connections, Perspect. Biol. Med. 31 (1988) 526–557.
[3] H. Vosgerau, Migraine therapy with magnesium glutamate, Ther Ggw 112 (1973) 640 passim.
[4] N.M. Ramadan, H. Halvorson, A. Vande-Linde, S.R. Levine, J.A. Helpern, K.M. Welch, Low brain magnesium in migraine, Headache 29 (1989) 590–593.
[5] A. Jain, N. Sethi, P. Babbar, A clinical electroencephalographic and trace element study with special reference to zinc, copper and magnesium in serum and cerebrospinal fluid (CSF) in cases of migraine, Neurol. Suppl. (1985) 232.
[6] A. Mauskop, B.T. Altura, R.Q. Cracco, B.M. Altura, Deficiency in serum ionized magnesium but not total magnesium in patients with migraines. Possible role of ICa2+/IMg2+ ratio, Headache 33 (1993) 135–138.
[7] V. Gallai, P. Sarchielli, G. Coata, C. Firenze, P. Morucci, G. Abbritti, Serum and salivary magnesium levels in migraine. Results in a group of juvenile patients, Headache 32 (1992) 132–135.
[8] V. Gallai, P. Sarchielli, P. Morucci, G. Abbritti, Red blood cell magnesium levels in migraine patients, Cephalalgia 13 (94) (1993) discussion 73.
[9] J.H. de Baaij, J.G. Hoenderop, R.J. Bindels, Magnesium in man: implications for health and disease, Physiol. Rev. 95 (2015) 1–46.
[10] L.G. Abbott, R.K. Rude, Clinical manifestations of magnesium deficiency, Miner. Electrolyte Metab. 19 (1993) 314–322.
[11] C. Sun-Edelstein, A. Mauskop, Role of magnesium in the pathogenesis and treatment of migraine, Expert Rev. Neurother. 9 (2009) 369–379.
[12] E. Loder, R. Burch, P. Rizzoli, The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines, Headache (52) (2012) 930–945.
[13] L. Teigen, C.J. Boes, An evidence-based review of oral magnesium supplementation in the preventive treatment of migraine, Cephalalgia 35 (2014) 912–922.
[14] A. Mauskop, J. Varughese, Why all migraine patients should be treated with magnesium, J. Neural Transm. (Vienna) 119 (2012) 575–579.
[15] A. Shahrami, F. Assarzadegan, H.R. Hatamabadi, M. Asgarzadeh, B. Sarehbandi, S. Asgarzadeh, Comparison of therapeutic effects of magnesium sulfate vs. dexamethasone/metoclopramide on alleviating acute migraine headache, J. Emerg. Med. 48 (2014) 69–76.
[16] M.E. Bigal, C.A. Bordini, S.J. Tepper, J.G. Speciali, Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study, Cephalalgia 22 (2002) 345–353.
[17] S. Demirkaya, O. Vural, B. Dora, M.A. Topçuoğlu, Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks, Headache 41 (2001) 171–177.
[18] Y. Cete, B. Dora, C. Ertan, C. Ozdemir, C. Oktay, A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department, Cephalalgia 25 (2005) 199–204.
[19] J. Corbo, D. Esses, P.E. Bijur, R. Iannaccone, E.J. Gallagher, Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache, Ann. Emerg. Med. 38 (2001) 621–627.
[20] L.R. Frank, C.M. Olson, K.B. Shuler, S.F. Gharib, Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial, CJEM 6 (2004) 327–332.
[21] S. Ginder, B. Oatman, M. Pollack, A prospective study of i.v. Magnesium and i.v. Prochlorperazine in the treatment of headaches, J. Emerg. Med. 18 (2000) 311–315.
[22] (IHS) HCCotIHS, The International classification of headache disorders, 3rd edition, (Beta Version). Cephalalgia 33 (2013), pp. 629–808.
[23] H. Hurst, J. Bolton, Assessing the clinical significance of change scores recorded on subjective outcome measures, J. Manipulative Physiol. Ther. 27 (2004) 26–35.
[24] J.T. Farrar, J.P. Young, L. LaMoreaux, J.L. Werth, R.M. Poole, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale, Pain 94 (2001) 149–158.
[25] M.C. Rowbotham, What is a "clinically meaningful" reduction in pain? Pain 94 (2001) 131–132.
[26] H. Choi, N. Parmar, The use of intravenous magnesium sulphate for acute migraine: meta-analysis of randomized controlled trials, Eur. J. Emerg. Med. 21 (2014) 2–9.
[27] S.L. Orr, B.W. Friedman, S. Christie, et al., Management of adults with acute migraine in the emergency department: the american headache society evidence assessment of parenteral pharmacotherapies, Headache 56 (2016) 911–940.
[28] M.J. Marmura, S.D. Silberstein, T.J. Schwedt, The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies, Headache 55 (2015) 3–20.