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Magnesium sulfate and acute migraine: a randomized clinical trial

Metoclopramide in managing acute migraine

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Abstract

Aim: In the current study we have aimed to evaluate the magnesium sulfate, as an adjuvant treatment, in managing acute migraine. Further knowledge of the migraine pathology elucidates the role of magnesium in the treatment of the disease.

Materials and Methods: Patients with migraine referred to Ahvaz Golestan Hospital emergency department were included in this randomized clinical trial. Patients' characteristics including gender, age, and weight were extracted from the files. Patients were randomly divided into two equal groups using block randomization method. Group A received 2 g intravenous infusion (I.V) of Magnesium sulfate along with 10 mg metoclopramide. And group B received 10 mg metoclopramide and placebo. The pain level was measured by NRS at baseline, 15, 30, and 45 minutes after intervention.

Results: Eighty patients were randomly assigned into two groups, forty (50%) were male. Most patients were between 30 and 40 years old. The baseline characteristics have not shown significant differences between the groups. The mean pain level at admission was not significantly different (9.94 and 10, respectively). Although pain reduction was significant in both groups, there was a significant difference between the two groups. The pain reduction slope in group A was significantly more severe.

Discussion: The findings of this study showed that the use of magnesium sulfate along with metoclopramide increased the effect of metoclopramide in managing acute migraine. However, our findings could not support the independent effect of magnesium sulfate on the reduction of migraine headaches.

Keywords

Acute Migraine; Headaches; Metoclopramide; Magnesium Sulfate; Clinical Trial; Emergency Department

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Introduction

Migraine is one of the main causes of primary and secondary headaches that affects about 70-80% of the world's population [1]. Migraine is the second most leading cause of headache, after tension headache. It is a neurobiological disorder caused by increased irritability of the central nervous system (CNS) and associated with periodic unilateral and pulsating headaches [2]. The prevalence of migraines has been reported by the International Headache Society (IHS) as 13% in Asia (3% in men and 10% in women). The scattering epidemiological reports of Iran have shown its prevalence from 6.1 to 15.5%, which is higher than in other Asian countries [3].

The most common symptoms are nausea, vomiting, photophobia, and phonophobia [4]. Although the main cause of migraine is unknown, several genetic and environmental predisposing factors have been reported [5]. Methylenetetrahydrofolate Reductase (MTHFR) gene mutations and increased homocysteine levels, abnormal levels of vitamin D, production of inflammatory substances around the nerves and cerebrospinal fluid, increased serotonin production from the platelets, increased vascular sensitivity to nitric oxide, and reduced levels of metabolic enzymes are the most known causes of migraine [6,7].

Choosing the optimal treatment for a patient depends on many factors, the most important of which is the severity of the pain. Migraine patients are normally managed with one of the three main drug groups including non-steroidal anti-inflammatory drugs (NSAID), -5HT1 agonists, and dopamine antagonists [8]. NSAIDs cause some potential side effects such as indigestion, gastrointestinal irritation. Because of the different side effects and inefficiency of these drugs, it is essential to discover new medication.

Recent studies have also shown that magnesium deficiency can play a major role in the pathophysiology of migraine [9]. The exact mechanism of magnesium effect is not fully understood, it affects the Na-K-ATPase pump and also sodium-potassium and calcium channels. It also reduces the release of acetylcholine at the site of the musculoskeletal system, thereby increasing vascular tone. The serotonin functions were also controlled by magnesium, thereby this intracellular cation affects many physiological processes [10]. There are about 24 grams of magnesium in the body which majorly located in bone and soft tissues, and less than 1% present in the circulation [11]. Evidence suggests that the level of magnesium in migraine patient's serum, blood cells, and cerebrospinal fluid is significantly lower than healthy people. On the other hand, trial studies have shown contradictory findings on the effect of magnesium infusion in alleviating migraine symptoms [12,13]. In the current study, we aimed to evaluate the magnesium sulfate, as an adjuvant treatment, in managing acute migraine.

Material and Methods

Study Design

This randomized clinical trial included patients with migraine that have referred to Ahvaz Golestan Hospital emergency department between October 2017 and November 2018. In this study, we aimed to compare the therapeutic effects of metoclopramide and magnesium sulfate along with metoclopramide in patients with acute migraine. Migraine diagnosis was carried out according to the International Crisis Association (CID) headache criteria. The study has been approved by Ahvaz Jundishapur University of Medical Sciences ethical committee (R.AJUMS.REC.1396.1142). The informed consent was signed by patients willing to participate in the study. The study was registered in Iran randomized clinical trial registry (IRCT).

Patients aged over 18 years with pain scores more than 4 (Measured by the Numerical Rating Scale (NRS)) and those who were willing to participate in the study were eligible candidates. The exclusion criteria were any history of drug adverse reactions such as gastrointestinal complications, pregnancy, lactation, renal failure, migraine headache for the first time, allergy to magnesium or metoclopramide, use of the medications for three consecutive days before the study.

Therapeutic intervention

Patients' characteristics including gender, age, and weight were extracted from the files. Before the beginning of the study, the patients were informed about the medical treatment procedure and side effects. All patients were observed by the emergency physician during the treatment. The subjects, a nurse who administrates the drug and also a physician who measures the pain level were not informed about the intervention type.

At the beginning of the study, the patients specified the level of the pain using NRS on a range of zero to ten which indicates no pain and the worst, respectively. Patients were randomly divided into two equal groups using block randomization method. Patients in group A received 2 g intravenous infusion (I.V) magnesium sulfate along with 10 mg metoclopramide. Patients in group B received 10 mg metoclopramide and placebo. The pain level was measured at baseline, 15, 30 and 45 minutes after the medication administration. Patients whose NRS score remained more than 4 or patients in whom the severity of headache did not decrease by 50% received half dose of medication after 15 and 30 min in both groups.

Statistical analysis

According to the Cete et al. study [14], with 95% confidence interval (95% CI) and accuracy of 5%, the minimum required sample size was calculated to be 80 persons (40 persons per group). All data were analyzed by descriptive statistics including mean, standard deviation (SD) and frequency. Independent t-test and the Mann-Whitney test were used to compare the mean based on the normality of the data. Multiple mean comparisons were done using the Tukey test. A Linear regression test was carried out to compare the slopes. All analyses were performed using SPSS version 22 software. A p- value less than 0.05 was considered significant.

Results

Eighty-eight patients were enrolled in the study, 8 of them were excluded due to pregnancy, renal failure, and allergy to metoclopramide and 80 patients were randomly assigned into two groups (Figure 1). Forty (50%) were male and 40 were female. Most patients were between 30 and 40 years old. The baseline characteristics have not shown significant differences between the groups (Table 1).

The medication side effects were not reported for any of the patients in both groups. In each of the groups A and B, three patients could not tolerate pain severity and received 5 mg

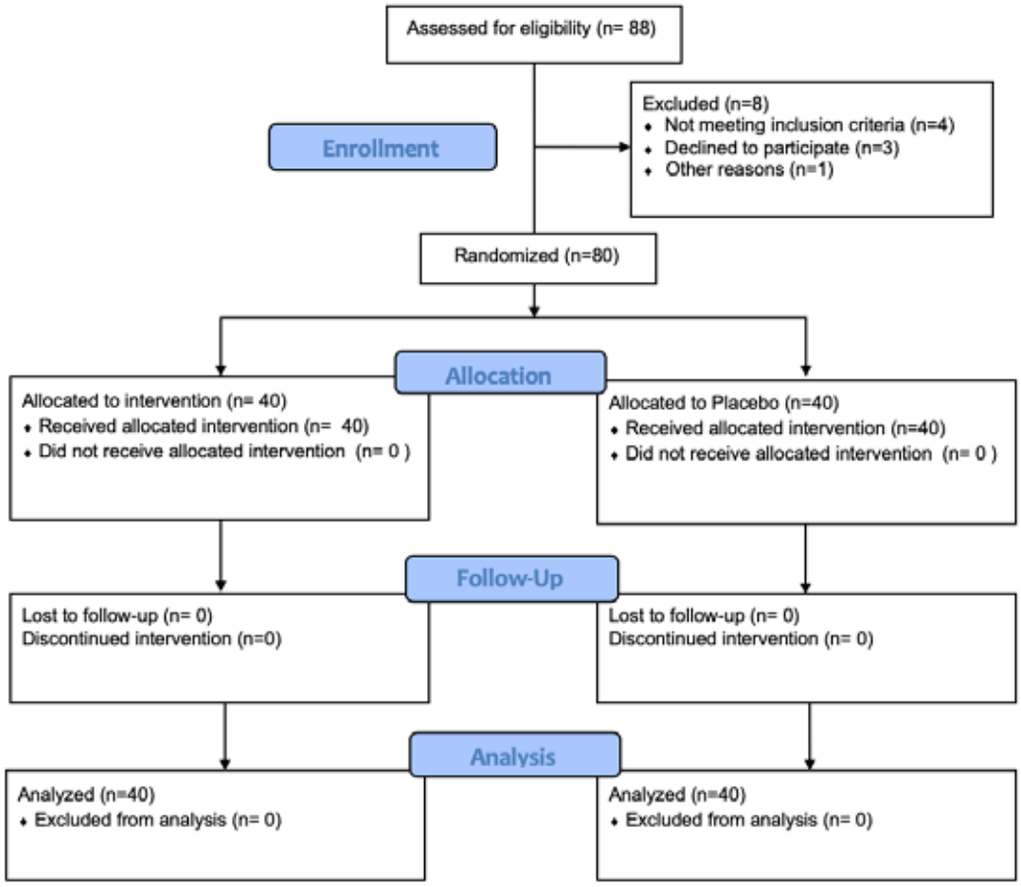
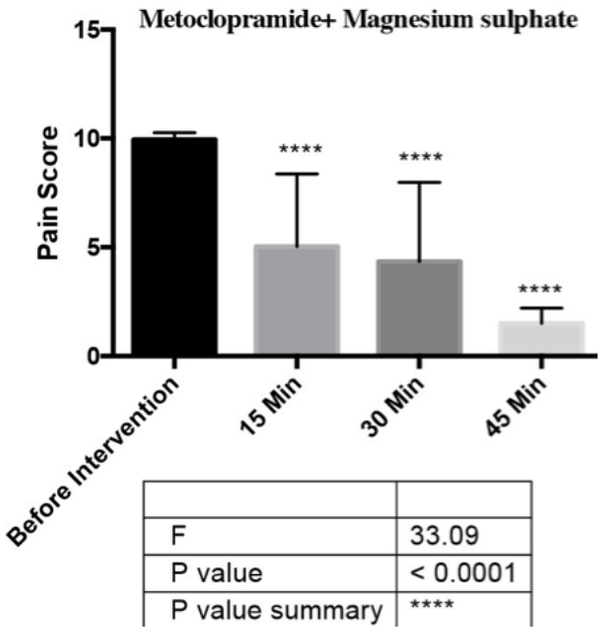
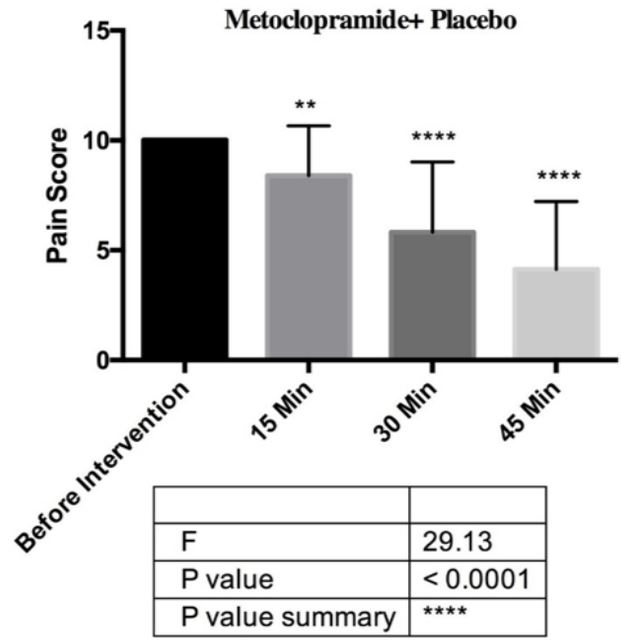


Figure1. Study design flowchart.



F	33.09
P value	< 0.0001
P value summary	****

Figure 2. Comparison of pain at different time points in the patients treated by Metoclopramid plus magnesium sulfate.



F	29.13
P value	< 0.0001
P value summary	****

Figure 3. Comparison of pain at different time points in the patients treated by metoclopramid plus placebo.

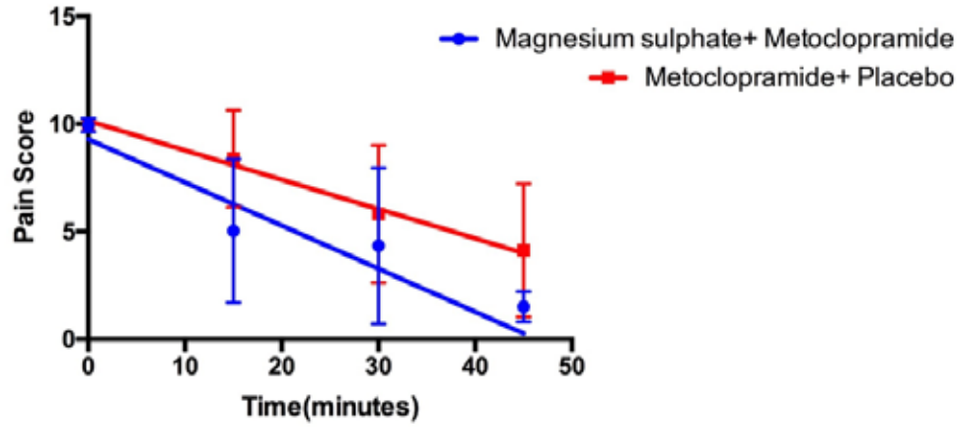


Figure 4. Comparison of pain reduction in both groups.

morphine as the rescue analgesic. They were excluded from the study after 30 minutes.

The mean pain level at admission in Group A and Group B were 9.94 and 10, respectively, which differences were not statistically significant. In both groups, pain level decreased significantly 15 minutes after intervention. However, the intensity of pain reduction was more severe in group A (Figure 2, Figure 3). Linear regression tests were used to compare pain reduction slope in both groups. Although pain reduction was significant in both groups, there was a significant difference between the two groups. The pain reduction slope in group A, was significantly more severe (Table 2) (Figure 4).

Table 1. Patient's characteristics

Variables	Group A	Group B	P value
		Age	
20-30 years	5(12.5%)	9(22.5%)	X2=1.56, df=2, p=0.45
31-40 years	21(52.5%)	17(42.5%)	
More than 40 years	14(35%)	14(35%)	
		Gender	
Male	20(50%)	20(50%)	p=1

Table 2. Comparison of pain reduction in both groups

Variables	Group A	Group B
Best-fit values		
Slope	-0.2005 ± 0.02325	-0.1364 ± 0.01465
Y-intercept when X=0.0	9.290 ± 0.4057	10.14 ± 0.3121
X-intercept when Y=0.0	46.34	74.34
1/slope	-4.989	-7.331
Male	20(50%)	20(50%)
95% Confidence Intervals		
Slope	-0.2467 to -0.1543	-0.1654 to -0.1074
Y-intercept when X=0.0	8.484 to 10.10	9.522 to 10.76
X-intercept when Y=0.0	39.55 to 56.92	63.78 to 90.42
Is slope significantly non-zero?		
F	74.32	86.67
DFn, DFd	1.000, 100.0	1.000, 119.0
P value	< 0.0001	< 0.0001
Deviation from zero?	Significant	Significant
Are the slopes equal?	F=5.82334 DFn=1 DFd=219 P=0.0166	

Discussion

Migraine headache is a common complication in patients referred to the emergency department and accounts from 1 to 2% of all referrals. For a long time, the standard treatment for migraine attacks in the emergency department was opioid analgesics. Recently, several treatments including metoclopramide, chlorpromazine, prochlorperazine, Sumatriptan, and Dihydroergotamine have been proposed for the treatment of migraines in the ED. Metoclopramide has become more accepted as a safe and effective treatment. At first, it has been used for nausea managing that is associated with migraine. Further studies showed that its dopamine antagonist quality may make it as an important treatment for acute migraine to relieve pain and nausea [15]. Metoclopramide at a dose of 10 to 20 mg could be effective in managing migraine headaches [2,16,17]. On the other hand, with further knowledge of the migraine pathology, the role of magnesium in the treatment of this disease has been increased. The mechanism of magnesium therapy for migraine is through its effect on serotonin function, as an important factor in developing migraine headaches. Magnesium can also help improve migraine symptoms by affecting the vascular tone (another important factor in developing a migraine headache). In a study by Massoud et al., the magnesium level in patients with migraine headache was evaluated. They have shown that the mean serum level of magnesium at the onset of headache was significantly decreased (P = 0.001) [18]. Moreover, several other studies declared the underlying role of magnesium in migraine pathophysiology. Even though migraine patients mostly referred to the emergency department, there is still no general agreement on the management of acute migraines [19]. In the present study, we have investigated the effect of magnesium sulfate as an adjunct to metoclopramide in migraine treatment.

The findings of this study showed that the use of magnesium sulfate significantly increases the metoclopramide effects on relieving migraine headache. Our results have shown that the pain reduction slope in the patients treated by metoclopramide along with magnesium sulfate was significantly more severe than those treated by metoclopramide alone. Magnesium sulfate also was used by Maleki et al. as an adjunctive drug in acute renal colic treatment, results of their double-blind clinical trial showed that magnesium sulfate did not have an effect on

renal colic pain reduce [20]. In a study by Shahrami et al., the therapeutic effect of magnesium sulfate versus dexamethasone/metoclopramide in the treatment of acute migraine was investigated and showing that magnesium sulfate reduced the severity of pain more effective than dexamethasone/metoclopramide [21]. The effects of magnesium on migraine pain reduction have also been shown in previous studies. In another RCT study, the effects of 1g of I.V magnesium versus I.V dihydroergotamine were compared and the results indicated that the effects of both medications are similar [22]. In another intervention study, it was shown that the administration of 600 mg of magnesium for 12 weeks significantly decreased the frequency and duration of migraine attacks, the severity of the headache and the use of anti-migraine drugs [23]. However, in these studies, the beneficial effect of magnesium sulfate on the management of acute migraine attacks has not been discussed. Contrary to our findings, Cete Y et al. failed to find any priority of magnesium sulfate therapeutic effect on alleviating migraine headache when compared with metoclopramide [14]. The contrary could be explained by the differences in treatment types. Although in our study magnesium sulfate was prescribed in combination with metoclopramide, Cete Y et al. administrated the drugs separately and in two groups. In another study by Corbo et al., similar to the current study, patients referred to the emergency department were treated with magnesium sulfate/metoclopramide or metoclopramide/normal saline for migraine headache. Contrary to our findings, they have concluded that the magnesium sulfate inhibited the metoclopramide effects; the percentage of patients with 50% VAS reduction was significantly lower in magnesium sulfate/metoclopramide recipients [24]. The statistical analysis approach in the study by Corbo et al. was very different from ours, which could be one of the most important causes of the contrary. In addition, in the Corbo's study, more than 95% of the patients were female, that caused selection error, while in our study we selected an equal number of male and female to eliminate the interventional effects of gender variable.

Conclusion

The findings of this study showed that the use of magnesium sulfate along with metoclopramide increased the effect of metoclopramide in managing acute migraine. However, our findings could not support the independent effect of magnesium sulfate on the reduction of migraine headaches. We have not evaluated the drugs related to adverse events and it was the major limitation of the study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards for research involving human subjects and has been approved by Ahvaz Jundishapor University of Medical Sciences ethical committee (R.AJUMS.REC.1396.1142). The informed consent was signed by patients willing to include in the study. The study was registered in Iran randomized clinical trial registry (IRCT).

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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