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Pharmacology in Emergency Medicine

COMPARISON OF THERAPEUTIC EFFECTS OF MAGNESIUM SULFATE VS. DEXAMETHASONE/METOCLOPRAMIDE ON ALLEVIATING ACUTE MIGRAINE HEADACHE

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□ **Abstract—Background: There is controversy about the efficacy of currently used treatment modalities to alleviate migraine headaches. Objective: We aimed to evaluate and compare the effects of magnesium sulfate and combined use of dexamethasone/metoclopramide on relieving acute migraine headache. Methods: We randomly divided 70 patients who had been referred to an emergency department, into two equal treatment groups with the two treatment plans, and analyzed pain severity at baseline using a numeric rating scale (NRS). We gave dexamethasone/metoclopramide to one group and magnesium sulfate to the other group, and evaluated pain severity at 20 min and at 1- and 2-h intervals after infusion. Finally, we used repeated-measure and two-way analysis of variance for intra- and inter-group evaluations of pain severity and complications, respectively. Results: We found no significant differences in demographic data and pain severity at baseline (8.2 vs. 8.0) between the two groups ($p < 0.05$). In the dexamethasone/metoclopramide group, pain severity (mean ± standard deviation) was 7.4 ± 1.4 ($p = 0.36$), 6.0 ± 2.4, and 2.5 ± 2.9 ($p < 0.0001$) at 20-min, 1-h, and 2-h intervals after treatment, respectively, with statistically significant differences between the baseline values and 1-h and 2-h interval values. Administration of magnesium sulfate was associated with decreased pain severity at the three intervals (5.2 ± 1.7, 2.3 ± 1.9, and 1.3 ± 0.66, respectively), exhibiting significant differences compared to baseline values and the corresponding time intervals in the dexamethasone/metoclopramide group ($p < 0.0001$). Conclusions: According to the results, magnesium sulfate was a more effective and fast-acting medication compared to a combination of dexamethasone/metoclopramide for the treatment of acute migraine headaches.** © 2015 Elsevier Inc.

□ **Keywords—migraine; treatment; magnesium sulfate; dexamethasone; metoclopramide**

INTRODUCTION

In some parts of the world, the prevalence of migraine headache is up to 17% in females and 6% in males, and migraines account for > 22 million years lost due to disability (1). Migraine headaches can be disabling, they can recur up to 15 times a month and significantly decrease the patient's quality of life (2). In addition, treatment costs of migraine are very high; European countries spend approximately 18.5×10^9 Euros on treating migraine headaches every year (3).

When the migraine headache does not respond to usual medications (eg, antihypertensive, anticonvulsive, or nonsteroidal anti-inflammatory agents), patients are referred to emergency units or similar urgent care centers,

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and usually receive intravenous medications (4–6). Routine procedures used to relieve severe and refractory migraine headaches in such settings include the administration of intravenous fluids, dihydroergotamine, dexamethasone, magnesium sulfate, and anti-emetic dopamine antagonists, such as metoclopramide (7–17).

Magnesium has a role in the pathogenesis of headache, migraine, and aura due to its vascular effects (15–17). Intravenous administration of magnesium promptly relieves 80% to 86% of various headaches (18). It has very minor side effects and there is a wide gap between its therapeutic dose and toxic dose (therapeutic index). In addition, when kidneys are healthy, magnesium toxicity is very rare (19). Dexamethasone is also very effective in relieving or decreasing recurrence rate of migraine headaches due to its anti-inflammatory effects (20–23). In addition, administration of 10 or 20 mg metoclopramide decreases the severity of migraine headaches (24,25).

Marx et al. suggest administration of intravenous dehydroergotamine (DHE) and metoclopramide (to treat the DHE-caused nausea and vomiting) in cases of moderate to severe migraine headache attacks. Sumatriptan, the first approved medication of the triptan class, is a selective 5-HT1B and 5-HT1D receptor agonist and has also been suggested by Rosen for acute treatment (26). These medications might not be readily available in all areas of the world and evaluation of more accessible therapies in needed.

In Iran, DHE and sumatripan have been replaced by dexamethasone, a steroid, in emergency departments. The use of steroids for treating migraine has been supported by anecdotal evidence that suggests they may be effective for prolonged migraine attacks refractory to standard therapies and for treating status migrainosus (26–28).

Although some studies showed metoclopramide and magnesium sulfate were effective in decreasing pain, other studies suggested that combination therapy with metoclopramide and magnesium sulfate decreased the efficacy of metoclopramide in relieving pain (29,30). Given the findings mentioned, evaluation of the efficacy of medications used in the treatment of migraine headaches requires more studies to derive a concrete and clear conclusion for treatment of migraine. Since magnesium sulfate has shown good accessibility, efficacy, and safety profile for the treatment of migraine, we aimed to compare the efficacy of combination therapy with dexamethasone/metoclopramide vs. magnesium sulfate (25). We undertook the present double-blind clinical trial to evaluate and compare the efficacy of these two strategies in the treatment of migraine headaches.

METHODS

Study Design

We designed a randomized, double-blind, clinical trial comparing the efficacy of dexamethasone/metoclopramide (8 mg dexamethasone and 10 mg metoclopramide) to magnesium sulfate (1 g in 100 mL normal saline) intravenously in the treatment of acute migraine. For ethical reasons, we did not have a placebo arm. This trial was approved by the Institutional Review Boards of Shahid Beheshti University of Medical Sciences, Tehran, Iran. We conducted the study in 2011.

Selection of Participants

We enrolled 70 patients older than 18 years of age who had been referred to the emergency department of an academic center in Tehran, Iran (Figure 1). An emergency room physician member of the team identified potential cases during shift work in the emergency department. This team member applied International Classification of Headache Disorders (ICHD) criteria, classified the headache, and alerted the research team on a potential subject. Our research team approached the patient for consent. The same emergency department physician established the diagnosis of migraine headache, based on ICHD criteria, listed as a form (31). These criteria were assessed for each patient. We randomly divided patients into two equal groups.

Inclusion criteria included the presence of headache at the time of administration of medicine, absence of previous treatment with antimigraine medications, absence of systemic diseases, and a numeric rating scale (NRS) score > 4 cm for the severity of headache. Exclusion criteria included inability to obtain/provide consent and lifetime history of fewer than five migraine attacks. We also excluded patients with hypersensitivity to metoclopramide, dexamethasone, magnesium sulfate, concurrent pregnancy, actively breastfeeding, history of renal insufficiency, use of other medications to relieve pain, and previous participation in the present study.

Intervention

After evaluation for inclusion and exclusion criteria, we randomized eligible patients using an online random-number generator to 1 of 2 treatment (by injection) groups: prepared solutions of dexamethasone/metoclopramide (8 mg dexamethasone and 10 mg metoclopramide in 100 mL normal saline solution, infused in 15 min) and magnesium sulfate (1 g in 100 mL normal saline, infused in 15 min).

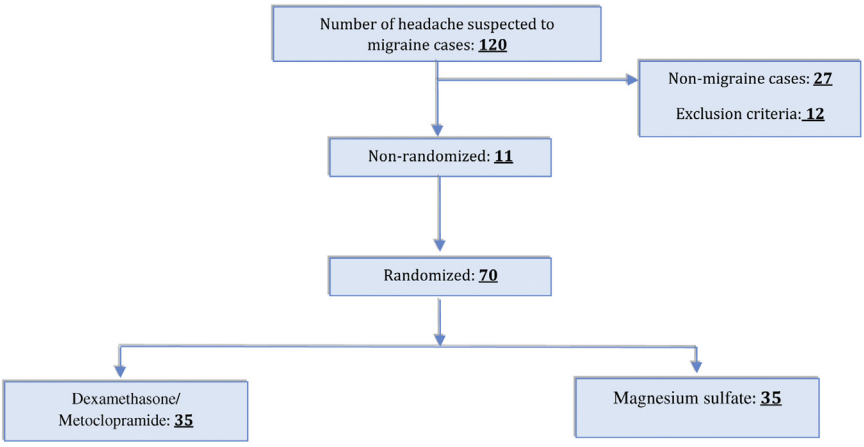

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart.

We balanced randomization by using permutated blocks of five and did not stratify for baseline characteristics. We also blinded patients and clinicians to study medication.

Subsequently, we collected data on response to treatment, relief of the symptoms, and potential side effects at 20-min, 1-h, and 2-h mark. We recorded the results in relevant charts. Three separate physicians prepared solutions, carried out the medication administration, and recording of results in effort to ensure the double-blind design of the study. Each research package appeared the same to the naked eye. We established a plan such that data on medications infused were only available to the therapeutic staff if complications or other adverse clinical changes occurred in patients. This was important to ensure patient safety.

If pain from migraine headache continued 20 min after administration of either of the investigational regimens, we allowed the physician in charge to order rescue medications. None of the subjects developed complications that required unblinding the data on which regimen was administered.

Methods of Measurement

We determined the pain score of the patients based on an 11-scale standard NRS (1). Patients were asked by a member of our research team to define their pain as a number between 0 and 10, with 0 representing no pain and 10 representing the worst pain imaginable. Pain was assessed at baseline and then reassessed 20 min, 1 h, and 2 h after medication administration. We performed the 2-h follow-up because it was a standard endpoint in outpatient migraine clinical trials (32).

We recorded adverse effects (eg, nausea, vomiting, vertigo, and lethargy) based on self-reports and clinical manifestations. After 2 h of follow-up, the patients were discharged by the physician in charge if pain had been achieved.

Effects of magnesium sulfate and dexamethasone/metoclopramide in decreasing migraine headache severity on NRS were 3.2 cm and 2.7 cm, respectively (21,28). Therefore, in this study, we calculated the sample size aiming to detect a change of at least 2 cm in the NRS scale; a magnitude in range with published literature, as well as one perceived to be clinically significant by our research team (33). With power set at 0.9 ($\beta = 0.01$) and error level at 0.05 ($\alpha = 0.05$), we estimated the minimum sample size for the study to be 31 subjects on each arm to detect a 2-cm difference in the pain intensity score (NRS at baseline vs. NRS at 2 h). We finally increased the sample size to 35 patients in each group to ensure adequate power.

Data Analysis

We analyzed data by SPSS 11.5 (IBM SPSS, Armonk, NY) and STATA 11.0 (StataCorp, College Station, TX) statistical software programs. We reported pain severity as mean $\pm$ standard deviation (SD) at a confidence interval of 95% at baseline and 20-min, 1-h, and 2-h intervals. We used *t*-test to evaluate age differences between the two groups. We used χ^2 test to evaluate the differences between the two groups in sex and the complications of the treatment procedures.

We used repeated-measures analysis of variance (ANOVA) to evaluate intragroup changes of pain severity in terms of time, and two-way ANOVA to evaluate inter-group differences. Even though pain scores could be described with nonparametric statistics, we used parametric tests because the distributions in both groups were normal based on Kolmogorov-Smirnov test ($p = 0.69$). We defined statistical significance at $p < 0.05$.

Table 1. Baseline Particulars of the Subjects in the Two Study Groups

Variable	Dexamethasone/ Metoclopramide	Magnesium Sulfate	*p* Value
Age (years)			
Mean (SD)	38 (11.2)	36 (12.6)	0.49
95% CI	(34.1–41.8)	(31.7–40.3)	
Sex, n (%)			
Male	14 (40)	19 (54.3)	0.23
Female	21 (60)	16 (45.7)	

CI = confidence interval; SD = standard deviation.

RESULTS

At the end of the study, we randomized the 70 patients into two groups. Patient ages in the groups receiving dexamethasone/metoclopramide and magnesium sulfate were mean ± SD of 38 ± 11.2 and 36 ± 12.6 years, respectively ($p = 0.49$). In the dexamethasone/metoclopramide and magnesium sulfate groups, 14 (40%) and 19 (54.3%) subjects were male, respectively ($p = 0.23$). Migraine headache severity scores were mean ± SD of 8.2 ± 1.3 and 8.0 ± 0.9 in the dexamethasone/metoclopramide and magnesium sulfate groups, respectively, with no significant differences between the two groups ($p = 0.34$) (Tables 1 and 2). Sixteen patients required additional medication, 7 in the magnesium sulfate group and 9 in the dexamethasone/metoclopramide group ($p = 0.57$).

Our evaluation of the initial outcome of the patients showed that 20 min after institution of treatment with dexamethasone/metoclopramide, the mean ± SD of pain severity decreased to 7.4 ± 1.4, revealing no statistically significant difference from the pain severity reported at baseline (8.2 ± 1.3; $p = 0.36$). However, we observed a significant decrease in pain severity 1 h after administration of dexamethasone/metoclopramide compared to baseline and 20-min interval ($p < 0.0001$ and $p < 0.036$, respectively). Two hours after administration of dexamethasone/metoclopramide, migraine headache severity decreased significantly to 2.5 ± 2.5, revealing significant differences from baseline, 20-min, and 1-h intervals after treatment ($p < 0.0001$). Figure 2 depicts the gradual decrease in pain severity reported by the patients undergoing treatment with dexamethasone/metoclopramide.

Contrary to patients undergoing treatment with dexamethasone/metoclopramide, administration of magnesium sulfate resulted in a significant decrease in pain severity at 20-min interval. As shown in Figure 2, pain severity decreased to 5.2 ± 1.7 at 20-min interval, demonstrating a significant difference from the pain severity at baseline ($p < 0.0001$). Pain severity decreased almost steadily at 1 h (2.3 ± 1.9) and 2 h (1.3 ± 0.60) intervals after treatment ($p < 0.0001$).

Table 2 lists changes in pain severity during 20-min and 1- and 2-h intervals after treatment. The table shows that treatment with magnesium sulfate was more effective in decreasing migraine headache severity. Magnesium sulfate was more effective in decreasing pain severity at 20-min and 1- and 2-h intervals after treatment ($p < 0.0001$) compared to treatment with dexamethasone/metoclopramide. Two-hour follow-up of patients showed the least pain severity 2 h after injection of magnesium sulfate in the present study (1.3 ± 0.66), revealing statistically significant differences at all the time points evaluated ($p < 0.0001$). As Figure 2 shows, the gradient of the curve in the magnesium sulfate group was almost steady; however, the gradient in the dexamethasone/metoclopramide group was low in the beginning, but increased after 1 h. Therefore, we concluded that it takes at least 1 h for dexamethasone/metoclopramide to begin their effect on decreasing migraine headache severity, however, magnesium sulfate promptly decreased pain severity and is more effective.

Table 2. Pain Severity of Patients After Treatment With Dexamethasone/Metoclopramide and Magnesium Sulfate

Time Interval	Dexamethasone/Metoclopramide	% Change*	Magnesium Sulfate	% Change*	*p* Value
Baseline					
Mean (SD)	8.2 (1.3)	—	8.0 (0.9)	—	0.34
95% CI	7.8–8.7	—	7.7–8.3	—	
20 min					
Mean (SD)	7.4 (1.4)	9.8	5.2 (1.7)	35	<0.0001
95% CI	6.9–7.9	—	4.6–5.8	—	
1 h					
Mean (SD)	6.0 (2.4)	26.8	2.3 (1.9)	71.25	<0.0001
95% CI	5.2–6.8	—	1.6–2.9	—	
2 h					
Mean (SD)	2.5 (2.9)	69.5	0.66 (1.3)	91.75	<0.0001
95% CI	1.5–3.5	—	0.2–1.1	—	

CI = confidence interval; SD = standard deviation.
* Change from baseline.

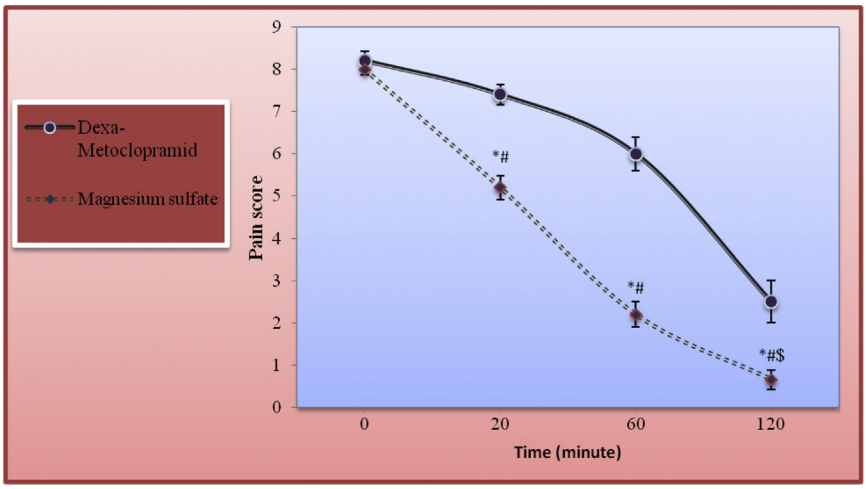

Figure 2. Changes in pain severity over time in patients undergoing treatment with dexamethasone/metoclopramide and magnesium sulfate. *Difference from dexamethasone/metoclopramide at the 20-min interval. #Difference from the dexamethasone/metoclopramide group at the 1-h interval. $Difference from the dexamethasone/metoclopramide group at the 2-h interval.

Although evaluation of complications did not reveal significant differences between the two study groups ($p = 0.78$), we had more patients with no complications (88.6%) in the magnesium sulfate group compared to those undergoing treatment with dexamethasone/metoclopramide (80.0%). In each group, 4 (11.4%) patients had nausea. In the dexamethasone/metoclopramide group, 1 (2.9%) patient experienced vomiting, 1 (2.9%) patient had vertigo, and 1 (2.9%) patient exhibited lethargy (Table 3).

DISCUSSION

Our present study suggests that intravenous infusion of magnesium sulfate provides faster and more effective symptom relief than combined therapy with dexamethasone/metoclopramide. In our study, use of magnesium sulfate resulted in a significant decrease in the mean pain severity at the 20-min interval; however, we did not observe a significant decrease in pain severity in patients undergoing treatment with a combination of dexamethasone and metoclopramide until the 1-h assessment.

Table 3. Complications Arising in Patients Undergoing Treatment With Dexamethasone/Metoclopramide and Magnesium Sulfate

Complications	Dexamethasone/ Metoclopramide, n (%)	Magnesium Sulfate, n (%)	*p* Value
Without complications	28 (80.0)	31 (88.6)	0.78
Nausea	4 (11.4)	4 (11.4)	
Vomiting	1 (2.9)	0 (0.0)	
Vertigo	1 (2.9)	0 (0.0)	
Lethargy	1 (2.9)	0 (0.0)	

The results of our study revealed 27% (2.2 cm) and 70% (5.7 cm) decreases in migraine headache severity at 1-h and 2-h intervals, respectively, after combined administration of dexamethasone and metoclopramide. Coppola et al. reported a 46% decrease in migraine headache severity score 1 h after administration of 10 mg intravenous metoclopramide (32). Jones et al. showed a 34% decrease in pain severity at 1 h with the same dose, and Corbo et al. reported an 82% decrease in pain severity at 2 h with the same dose (30,34). These observations suggest that in our study, combined administration of dexamethasone/metoclopramide was less effective than magnesium sulfate, and was less effective than in earlier studies using metoclopramide alone. It is possible dexamethasone decreases the efficacy of metoclopramide in the treatment of migraine headaches. A study reported by Corbo et al. showed lower efficacy of metoclopramide when used as combination therapy with magnesium sulfate compared to when metoclopramide was used alone (30). In our study, metoclopramide was used in combination therapy with dexamethadone, not magnesium sulfate. However, interestingly, we observed a similar damp down in its effect.

Despite the limited number of studies demonstrating a rapid effect of dexamethasone on decreasing migraine headache severity, the majority of studies, including those by Jones et al., Rowe et al., Friedman et al., and Baden and Hunter, have shown a delayed effect of dexamethasone in decreasing pain severity, and have emphasized the preventive role of dexamethasone in the recurrence of the disease (9,20,35–37). Based on these studies, dexamethasone reduces migraine headache severity through its anti-inflammatory effect in the nervous system. Since anti-inflammatory effects are usually

manifested with some delay and activation of intracellular mechanisms is necessary, our results support a delayed rather than rapid response at best (38).

Various studies on the administration of dexamethasone, metoclopramide, and magnesium sulfate to relieve migraine headaches have yielded different and, in some cases, contradictory results. Differences may be attributed to differences in methodologies. In addition, differences in medication regimens and doses used likely contributed to differences in the efficacy of medications. The development of a standard regimen to serve as control arm may allow more coherent and comparative results. Finally, most studies fail to exclude patients with transformed migraines. These patients do not respond well to medicinal treatment modalities, which might contribute to the excessive use of migraine medicines (39). Standardization of criteria and methodology would be beneficial to the development of treatment protocols for migraine headaches with better confidence and certainty.

A closer look at Figure 2 might lead to the conclusion that the gradient of the curve has increased after 1 h in the dexamethasone/metoclopramide group and further follow-up might have shown that this treatment modality is more effective than magnesium sulfate alone. This theory might be correct, but the importance of time should be taken into account. Migraine patients suffer from excruciating pain and measures of rapid alleviation of pain are considered a top priority. Our results suggest magnesium sulfate is more effective in decreasing pain severity during the first 2 h after patient presentation compared to dexamethasone/metoclopramide.

Finally, magnesium sulfate has a better safety profile when recurrence and chronicity are taken into account. Even though complications after a single dose of dexamethasone, metoclopramide, or magnesium sulfate would be rare, the long-term effects of these medications must be considered in migraine patients due to the high frequency of recurrence. Repeated use of dexamethasone increases the risk of osteoporosis, cataract, and immunodeficiency. Metoclopramide intervenes with the majority of sedatives, such as anticonvulsants, antihistamine, and antidepressants, which are known as oral migraine medications and their use during pregnancy must be supervised by a physician. In contrast, contraindications reported for the use of magnesium sulfate are limited to breastfeeding, renal insufficiency, and cardiac dysrhythmias. Furthermore, no side effects have been reported with the administration of 1-g dosing of magnesium sulfate or with recurrent administration (8,22,23).

Limitations

The first limitation of our study was the short follow-up period. In this context, 1- and 2-day and even 1-week follow-up of the patients might have provided the opportunity to evaluate the effect of these medications on the recurrence rate of headaches. Another limitation was the absence of a placebo group or standard arm. Due to ethical considerations, we could not follow the patients for 2 h without any medicinal intervention and with reliance only on placebo. On the other hand, since the majority of studies have shown that the effects of dexamethasone, metoclopramide, and magnesium sulfate differ from placebo, we did not include a placebo group in the study. Other than the cutoff of 2 h (1.84 cm), between the two groups, there is a > 2-cm difference. This difference is clinically significant because the rapid relief of pain is important in the emergency department. Therefore, magnesium sulfate seems to be a better medication.

CONCLUSIONS

Our present study is the first double-blind clinical trial comparing combination therapy with dexamethasone/metoclopramide to magnesium sulfate on alleviating acute migraine headache in the emergency department setting. We conclude that magnesium sulfate is faster acting and more effective than dexamethasone/metoclopramide in the treatment of acute migraine headache. Also, that combination therapy with dexamethasone/metoclopramide may not be superior to metoclopramide alone. The mechanism is unclear, but is it possible that dexamethasone decreases the efficacy of metoclopramide when treatment is combined. Further studies are required to test this hypothesis. Since dexamethasone, as an anti-inflammatory, may have a larger role in delayed effect or prevention of recurrence compared to metoclopramide or magnesium sulfate, we suggest future studies obtain a longer follow-up. Our results are of particular interest for settings in which newer agents or modalities are not readily available.

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ARTICLE SUMMARY

1. Why is this topic important?

Treating migraine is expensive everywhere, and European countries spend approximately 18.5×10^9 Euros annually for this treatment. This research attempts to find a less expensive treatment modality that would have fewer side effects and would be accessible in less-developed countries.

2. What does this study attempt to show?

The study evaluates and compares the administration of magnesium sulfate (which is accessible, inexpensive, has few side effects, and good previous reports) to combined administration of dexamethasone and metoclopramide (currently widely used in the practice of emergency medicine across our country) for the treatment of migraine headaches.

3. What are the key findings?

Dexamethasone/metoclopramide combination decreased pain scores. In this group, mean ± standard deviation pain severity scores were 7.4 ± 1.4 ($p = 0.36$), 6.0 ± 2.4, and 2.5 ± 2.9 ($p < 0.0001$) at 20-min, 1-h, and 2-h intervals after treatment, respectively. Differences were statistically significant between the baseline values and 1- and 2-h interval values. However, the magnitude of decrease in pain scores is lower than reported in published literature for metoclopramide alone. Magnesium sulfate more efficient and faster acting. In this group, mean ± standard deviation pain severity scores were 5.2 ± 1.7, 2.3 ± 1.9, and 1.3 ± 0.66, respectively. Differences were statistically significant compared to baseline values and the corresponding time intervals in the dexamethasone/metoclopramide group ($p < 0.0001$).

4. How is patient care impacted?

The results of the present study showed that magnesium sulfate is a more effective and faster-acting medication compared to a combination of dexamethasone/metoclopramide in the treatment of acute migraine headaches. It also has fewer side effects.