ORIGINAL RESEARCH

Comparison of Intravenous Metoclopramide and Acetaminophen in Primary Headaches: a Randomized Controlled Trial

Gholamreza Faridaalaee[1], Seyed Hesam Rahmani[1], Hamidreza Mehryar[1], Shahab Bina Shishavan[*1], Seyedeh Zahra Merghati[2], Mohammad Amin Valizade Hasanloei[3], Bahman Naghipour[4], Farzad Rahmani[5]

1. Department of Emergency Medicine, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, IR Iran.
2. Department of Internal Surgery, School of Nursing and Midwifery, International branch of Urmia University of Medical Sciences, Urmia, IR Iran.
3. Department of Anesthesiology, Urmia University of Medical Sciences, Urmia, IR Iran.
4. Department of Anesthesiology, Tabriz University of Medical Sciences, Tabriz, IR Iran.
5. Department of Emergency Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

*Corresponding Author: Bina Shishavan Shahab, Department of Emergency Medicine, Imam Khomeini Hospital, Ershad Avenue, Urmia, Iran.
Tel: +989141889486; Fax: +984433457286; Email: shahabbina@gmail.com
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Abstract

Introduction: Headache is the most common neurologic symptom among referees to the emergency department (ED), while the best treatment has not yet been found. Therefore, in the present study pain relief effects of metoclopramide and acetaminophen were compared in patients suffered acute primary headache. **Methods:** This study was a double-blind randomized clinical trial performed in Imam Khomeini Hospital, Urmia, Iran, through July to October 2014. All adult patients, with acute primary (migraine, tension type and cluster) headache referred to the ED were included in this study. Pain severity was measured with 10 centimeters numeric rating scales. The patients were randomized into two groups of intravenous (IV) metoclopramide (10 milligrams) and acetaminophen (1 gram). Pain score, success rate, and drug complications were compared between the 2 groups at 0, 15, 30, 60, and 120 minutes after injection. **Results:** 100 patients were equally categorized into two groups (mean age of 32 ± 13.2 years; 51.2% male). Initial pain score in metoclopramide and acetaminophen groups were 9.1 and 9.4, respectively (p = 0.46). IV metoclopramide did not have any analgesic effect at 15 minutes, but had good effect at 30 minutes. While, the analgesic effect of acetaminophen initiated after 15 minutes. After 2 hours, both drugs had good therapeutic effect on primary headaches (p < 0.001). **Conclusion:** The present study demonstrated that efficacy of metoclopramide for pain relief in primary headaches is lower than acetaminophen. In this regard, success rate of acetaminophen was 42.0% versus 0% for metoclopramide within 15 minutes. The efficacy of acetaminophen continued until 60 minutes.

Key words: Metoclopramide; acetaminophen; headache; migraine; acute pain

Introduction:

Headache is one of the most common neurologic symptoms among patients admitted to the emergency department (ED), as 3 million patients are annually visited only in the EDs of United States (1, 2). The disease is categorized into primary (such as migraine, tension type, and cluster) and secondary (such as those following intracerebral hemorrhage, trauma, tumor, etc.) groups. Primary is the most frequent type seen in EDs and 90% of them include migraine, tension, or even a combination of them (3, 4). Approximately, 12%

of general population suffer from migraine and acute exacerbations cause severe and disabling disorders (5-7). Several agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antiemetics, antipsychotics, etc. have been used for treatment (8). Recently, the use of dopamine antagonists, such as metoclopramide (alone or in combination with other drugs), and serotonin agonists, like sumatriptan, for this purpose has increased (9, 10). Administration of metoclopramide relieves the intensity of headaches; however, its efficacy varies among studies. For example, while, Tec et al. declared an ac-

ceptable therapeutic effect for metoclopramide in primary headaches, Coppola et al. deemed its efficacy to be equal to placebo (4, 11, 12). Given the above results, evaluation of metoclopramide's efficacy in management of primary headaches requires more studies to derive a concrete and clear conclusion. Therefore, the present study aimed to compare analgesic effects of intravenous (IV) metoclopramide and acetaminophen for acute primary headaches.

Methods:

Study design and setting

This study was a double-blind randomized clinical trial performed in Imam Khomeini Hospital, Urmia, Iran, through July to October 2014. The effect of IV metoclopramide (10 milligrams) and acetaminophen (1 gram) in treatment of acute headaches was compared. For ethical reasons, there was no placebo arm. The study protocol was confirmed by Ethical Committee of Urmia University of Medical Sciences and informed consent was obtained from patients. This protocol was registered in Iranian Registry of Clinical Trials with IRCT Number: IRCT2014081817812N3.

Subjects

Patients with acute primary headache and pain severity over 4 based on numeric rating scale (NRS), who were referred to the ED and did not have any systematic disease, were included. Exclusion criteria were having allergy to metoclopramide and acetaminophen, hepatic failure, secondary headache, pregnancy, breast-feeding, renal insufficiency, arbitrary treatment, and the case of recurrent headache. Migraine, tension type, and cluster headaches were diagnosed based on International Headache Society's International Classification of Headache Disorders (ICHD) criteria (13).

Intervention

The patients were randomized into two groups of metoclopramide (intervention group) with dosage of 10 milligrams, IV, in 2 minutes and acetaminophen group (control group) with dosage of 1 gram, slow IV, in 10 minutes. Randomization was performed by block randomization (size of 5 for blocks), using an online random number generator (RNG). Solutions were prepared by an independent pharmacist and kept in a sealed envelope. Drugs were injected by a physician blinded to the studied groups. Response to treatment and the side effects were assessed within 15, 30, 60, and 120 minutes after receiving medications and then compared with the baseline. The ED staff were blinded to composition of solutions and studied groups. The data of the prescribed solution were only available for the staff when drug complications and other adverse effects appeared in patients and the patient was excluded from the study. Rescue dose was prescribed, if the pain continued after 30 minutes from first drug administration. The disclosure of the data

about the prescribed medicine(s) was not required during the study period.

Measurements

11-scale standard numeric rating scale (NRS) was used to assess the pain score of patients (14). Patients were given a score number between 0 and 10, 0 representing no pain and 10 demonstrating the worst conceivable pain. Pain severity was assessed in the baseline (administration time) and then reassessed 15, 30, 60, and 120 minutes after medication. This follow up was performed because 120 minutes is a more standard endpoint for outpatient migraine trials (15). Nausea, vomiting, vertigo, and lethargy were recorded as adverse effects based on self-reports and clinical manifestations. Therapeutic success rate was defined as decreasing pain score to at least 3.

Statistical analysis

The minimum required sample size for the present study considering the clinically significant change of 2 scores in pain severity, standard deviation of 2.7 and 1.2 centimeters for effects of metoclopramide and acetaminophen in decreasing headache, power of 90% ($\beta=0.1$) and the error rate of 5% ($\alpha=0.05$) was estimated to be 33 subjects (16, 17).

Data were analyzed using SPSS 21. Quantitative variables were reported as mean and standard deviation and qualitative ones as frequency and percentage. Chi-square and Fisher exact tests were also used for comparison of basic characteristics of the two groups. Because data was not normally distributed, the comparison between pain severity changes in patients was performed using Wilcoxon-rank test. The success rate was reported as frequency and percentage as well as comparison of time changes between two therapies performed by non-parametric test for trend, which is an extension model of the Wilcoxon rank-sum test. Since some basic features between two therapeutic groups had significant difference, general linear model was done to find if success rate had significant difference after moderating these factors. $P < 0.05$ was considered as a significant level.

Results:

100 patients were equally categorized into two groups of IV acetaminophen and metoclopramide (mean age of 32 ± 13.2 years; 51.2% male). Table 1 shows demographic data of patients. As can be seen, age distribution of the two groups was significantly different ($p < 0.001$). Most migraine sufferers received IV acetaminophen, while patients with tension headache mostly took metoclopramide (Table 1, $p < 0.001$). The pain severity at administration time had no difference between the groups ($p = 0.46$). However, the mean pain severity at 15 minutes after taking acetaminophen was significantly less than metoclopramide group (7.0 ± 1.4 versus 9.0 ± 1.3, $p < 0.001$). This pattern was seen within 30 minutes (4.5 ± 2.0 versus 6.6 ± 1.5; $p < 0.001$), 60 minutes (3.1 ± 2.1 versus 5.4 ± 1.6; $p < 0.001$), and even 120

Table 1: Comparison of demographic data between two studied groups

Variable	Acetaminophen	Metoclopramide	p[1]
Age (year)			
<18	7 (43.8)	9 (56.2)	<0.001
18-40	43 (67.2)	21 (32.8)	
41-60	0 (0.0)	18 (100.0)	
61-75	0 (0.0)	2 (100.0)	
Gender			
Male	22 (51.2)	21 (48.8)	
Female	28 (49.1)	29 (50.9)	0.84
Marital status			
Single	15 (53.6)	13 (46.4)	0.66
Married	35 (48.6)	37 (51.4)	
Type of headache			
Migraine	35 (67.3)	17 (32.7)	
Tension type	8 (23.5)	26 (76.5)	<0.001
Cluster	7 (50.0)	7 (50.0)	

1, Based on Chi-Squared test; 2, based on Fisher exact test.

Table 2: comparison of pain score and successes rate in medical interventions between studied groups

Time (minute)	Acetaminophen		Metoclopramide		p[1]
	Mean ± SD	Success rate (%)	Mean ± SD	Success rate (%)	
Baseline	9.4 ± 0.7	----	9.1 ± 1.3	----	0.46
15	7.0 ± 1.4	21 (42.0)	9.0 ± 1.3	0 (0.0)	<0.001
30	4.5 ± 2.0	50 (100.0)	6.6 ± 1.5	34 (74.0)	<0.001
60	3.1 ± 2.1	50 (100.0)	5.4 ± 1.6	47 (94.0)	<0.001
120	1.5 ± 1.2	50 (100.0)	3.6 ± 2.0	50 (100.0)	<0.001

1, Based on Kruskal-Wallis equality of populations rank test; SD: Standard deviation.

Table 3: results of multivariate analysis for comparison of success rate between two groups

Time (minute)	Odds ratio	95% CI	p[1]
15	1.43	1.21-1.73	<0.001
30	1.38	1.17-1.64	<0.001
60	1.10	1.01-1.26	0.04

1, Based on general linear model adjusted for age and type of headache; CI: Confidence interval.

minutes (3.6 ± 2.0 versus 1.5 ± 1.2; p < 0.001) after injection (Table 2).

21 (42%) patients in acetaminophen group had significant pain relief, while none of subjects in metoclopramide group had such effectiveness in 15 minutes after medication. The 30-minute success rate for acetaminophen and metoclopramide groups were 100% and 74%, respectively. 100% therapeutic success rate in IV acetaminophen remained until 120 minutes (Table 2, p = 0.001). No side effect was seen among patients. Only 3 (6%) patients of metoclopramide group needed the rescue dose. After adjustment of analysis for basic charac-

teristics, the rate of therapeutic success for IV acetaminophen at 15 minutes (OR=1.43; 95% Cl=1.2-1.7; p < 0.001), 30 minutes (OR=1.38; 95%Cl=1.17-1.64; p < 0.001), and 60 minutes (OR=1.10; 95% Cl=1.01-1.26; p = 0.04) was more than metoclopramide (Table 3).

Discussion:
Based on the present study and similar to other major studies, metoclopramide had a pain relief effect on primary headaches, but in contrast to other researches, here metoclopramide had inferior effect to acetaminophen. It can be justified under racial differences. Several studies have been performed regarding therapeutic effects of metoclopramide on the primary headaches with

different results. While some of them showed good efficacy of metoclopramide for primary headaches, others concluded no efficacy. Salazar-Zúñiga and Garfias-Arvizu compared metoclopramide and sumatriptan in migraine sufferers and demonstrated that metoclopramide is more effective (18). Tec et al. showed that metoclopramide has therapeutic effects on headache, alone (4). Coppola et al. compared prochlorperazine, metoclopramide, and placebo; they showed that prochlorperazine has therapeutic effects on headache, but metoclopramide is more effective than placebo (9). In contrast, Cameron et al. compared prochlorperazine and metoclopramide, and demonstrated that prochlorperazine and metoclopramide are both effective on acute migraine headaches (19). Colman et al. concluded that metoclopramide is effective on the migraine especially in combination with other agents (20). Friedman et al. stated that a combination of metoclopramide and diphenhydramine are more effective than ketorolac for headaches (21). In another study, Friedman et al. compared 10 milligrams of IV prochlorperazine and combination of 20 milligrams metoclopramide and 25 milligrams diphenhydramine for acute migraine headaches. They showed prochlorperazine and combination of metoclopramide and diphenhydramine have the same effect for acute migraine headaches (22). In another study, Friedman et al. displayed 10 metoclopramide are more efficient than 30 milligrams ketorolac or 1000 milligrams valproate sodium (23). Weinman et al. performed a systemic review to find an effective drug for tension type of headaches and reviewed 8 studies. Their results were as below: metamizole, chlorpromazine, and metoclopramide are more effective than placebo for acute pain. The combination of metoclopramide with diphenhydramine has superiority to ketorolac. mepivacaine, meperidine with promethazine, and sumatriptan are not more effective than placebo (24). The results of this study had some similarities and dissimilarities with other studies. Variances in regimens and doses of medications can result in different efficacy of medications, so that use of one standard regimen may lead to results that are more coherent. Extrapyramidal reactions are one of the most important side effects of metoclopramide, which have been reported in nearly 10% of cases. For example, Coppola et al. demonstrated 2.5% of patients displayed dystonia or akathisia in initial minutes of drug administration (12). Also Friedman et al. stated that akathisia developed in 9.3% of patients (25). However, no side effect was found in the present study. There were several limitations in this study. The first limitation was the short follow-up period. Although, during 2 hours follow up no side effect was observed, the longer period such as 1or 2 days and even 1week follow up might have provided a better opportunity to evaluate long-term side effects and headache recurrence. Another limitation was single-blinded design of the trial. We were unable to do the study in a double-blinded way, because the routes of administration for drugs were different. Moreover, the lack of a placebo group or standard arm due to ethical consideration was also considered as another limitation.

Conclusion:

The present study demonstrated that efficacy of metoclopramide in pain relief of headaches is lower than acetaminophen. In this regard, success rate of acetaminophen in pain relief was 42.0%, while it was 0% for metoclopramide within 15 minutes. The efficacy of acetaminophen continued until 60 minutes.

References:

1. Taylor FR. Diagnosis and classification of headache. Prim Care. 2004;31(2):243-59.
2. McCaig LF, Nawar EW. National hospital ambulatory medical care survey: 2004 emergency department summary: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2006. p. 372.
3. Friedman BW, Hochberg ML, Esses D, et al. Applying the International Classification of Headache Disorders to the emergency department: an assessment of reproducibility and the frequency with which a unique diagnosis can be assigned to every acute headache presentation. Ann Emerg Med. 2007;49(4):409-19.
4. Tek DS, McClellan DS, Olshaker JS, Allen CL, Arthur DC. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. Ann Emerg Med. 1990;19(10):1083-7.
5. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007;47(3):355-63.
6. Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. N Engl J Med. 2002;346(4):257-70.
7. Wood AJ, Goadsby PJ, Lipton RB, Ferrari MD. Migraine—Current Understanding and Treatment. N Engl J Med. 2002;346(4):257-70.
8. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med. 2002;39(3):215-22.
9. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-

controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. Ann Emerg Med. 1995;26(5):541-6.

10. Talabi S, Masoumi B, Azizkhani R, Esmailian M. Metoclopramide versus sumatriptan for treatment of migraine headache: A randomized clinical trial. J Res Med Sci. 2013;18(8):695.

11. Ashina S, Portenoy RK. Intravenous treatment of migraine. Tech Reg Anesth Pain Manag. 2012;16(1):25-9.

12. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. Annals of emergency medicine. 1995;26(5):541-6.

13. Olesen J, Steiner T. The International classification of headache disorders, 2nd edn (ICDH-II). J Neurol Neurosurg Psychiatry. 2004;75(6):808-11.

14. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27(4):485-9.

15. Tfelt-Hansen P, Block G, Dahlöf C, et al. Guidelines for controlled trials of drugs in migraine. Cephalalgia. 2000;20(9):765-86.

16. Turkcuer I, Serinken M, Eken C, et al. Intravenous paracetamol versus dexketoprofen in acute migraine attack in the emergency department: a randomised clinical trial. Emerg Med J. 2014:182-5.

17. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ. 2008;336(7657):1359-61.

18. Salazar-Zúñig A, Garfias-Arvizu A. Management of the acute migraine episode with sumatriptan vs. metoclopramide. Rev Biomed. 2006;17:175-82.

19. Cameron JD, Lane PL, Speechley M. Intravenous chlorpromazine vs intravenous metoclopramide in acute migraine headache. Acad Emerg Med. 1995;2(7):597-602.

20. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. BMJ. 2004;329(7479):1369-73.

21. Friedman BW, Adewunmi V, Campbell C, et al. A randomized trial of intravenous ketorolac versus intravenous metoclopramide plus diphenhydramine for tension-type and all nonmigraine, noncluster recurrent headaches. Ann Emerg Med. 2013;62(4):311-8. e4.

22. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. Ann Emerg Med. 2008;52(4):399-406.

23. Friedman BW, Garber L, Yoon A, et al. Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. Neurology. 2014;82(11):976-83.

24. Weinman D, Nicastro O, Akala O, Friedman BW. Parenteral treatment of episodic tension-type headache: a systematic review. Headache. 2014;54(2):260-8.

25. Friedman BW, Mulvey L, Esses D, et al. Metoclopramide for acute migraine: a dose-finding randomized clinical trial. Ann Emerg Med. 2011;57(5):475-82.e1.