

Original Article

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Comparing the Therapeutic Effects of Dexamethasone-Metoclopramide with Ketorolac in Relieving Headache in Patients with Acute Migraine Attacks Presenting to the Emergency Department

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Abstract

Introduction: Migraine is a frequent chief complaint of patients in the emergency department. A wide range of treatments are used for acute migraine.

Objective: This study aimed to compare the therapeutic effects of a combination of metoclopramide + dexamethasone with those of ketorolac for treatment of acute migraine in the emergency department.

Method: This quasi-experimental study enrolled patients identified as migraine headache cases admitted to the emergency departments of Shohadaye Tajrish and Sina hospitals, Tehran, Iran. The patients were divided into two groups and treated with either 8 mg Dexamethasone + 10 mg Metoclopramide or 60 mg ketorolac, and then compared regarding the rate of pain control based on visual analogue scale (VAS) on arrival and 1 and 2 hours afterward.

Results: Overall, 86 patients were recruited, of whom 50 were male (58.1%). Their mean age was 37.6 ± 10.3 years. Thirty-five (40.7%) were in the ketorolac group and 51 (59.3%) were in the dexamethasone + metoclopramide group. Treatment success was defined as a reduction of at least 3 points in pain severity in comparison to the admission time. One hour after administration of medications, the reported pain intensity was 4.7 ± 2.0 and 6.2 ± 2.3 in ketorolac group and dexamethasone + metoclopramide group, respectively. By the second hour, pain intensity was 3.4 ± 1.2 and 2.9 ± 1.3 in ketorolac group and dexamethasone + metoclopramide group, respectively. The two groups did not show a significant difference in terms of the reported pain at this time ($p=0.04$).

Conclusion: Based on our findings, the pain reduction time was relatively shorter for ketorolac in acute migraine, but the final response was identical in the two groups.

Key words: Dexamethasone; Emergency Department, Hospital; Ketorolac; Metoclopramide; Migraine Disorders; Pain Management

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INTRODUCTION

Headache is a frequent complaint among patients presenting to the emergency department (ED), and migraine is one of its major causes. Migraine is a chronic and recurrent disease. It is characteristically a pulsatile and unilateral headache with an intensity of moderate to severe, and an atypical migraine attack lasts for 4 to 72 hours (1). Migraine headaches affect around 11%-12% of the US population and about 14% of the Iranians. It is more common among women, and typically begins in adolescence (2, 3). There are two types of therapies namely acute management and prophylactic therapy (4). In addition to conducting the diagnostic process, it is important

for an emergency physician to perform acute pain management with an available, cost effective, and appropriate medication. Many medications can be used in ED, and their difference lies in their availability, cost, and side effects. Some of these agents include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergothamin, triptans, valproic acid and steroids (5). Although dihydroergothamin and triptans are first line therapies in this regard, their use is sometimes limited due to their cost and limited availability. Therefore, an effective alternative treatment is needed. In developing countries like Iran, the most widely used agents are NSAIDs, steroids, and some

other medications to relieve vomiting and nausea such as metoclopramide. It appears that the most common NSAID used in Iran is ketorolac. It is available in two forms of intramuscular (IM), and intravenous (IV) in all EDs, but it is relatively contraindicated in patients with gastrointestinal bleeding, ischemic heart disease, renal failure, and allergy to NSAIDs (6). Instead, metoclopramide and dexamethasone are both used in such situations and have some reported benefits. Dexamethasone is frequently used for reducing recurrent pain in migraine patients. Metoclopramide is available in almost all EDs, and is used as an abortive migraine pain killer, but may result in extrapyramidal side effects in some instances (7). The purpose of this study is to compare the efficacy of combination therapy of metoclopramide-dexamethasone with that of parenteral ketorolac in patients with acute migraine headache presenting to ED.

METHODS

Study design

A multi-centered quasi-experimental study was conducted in 2015, in EDs of Shohaday Tajrish and Sina hospitals, the teaching hospitals of Shahid Beheshti and Tehran universities of medical sciences. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1394.189). Written informed consent for participation in the study was obtained from each participant. The researchers fully adhered to the Declaration of Helsinki Principles throughout the study.

Study population

Patients older than 18 years presenting to the EDs with the chief complaint of headache were interviewed and recruited if they met the diagnostic criteria for acute migraine headache according to International Classification of Headache Disorder-3 (ICHD-3). The participants were evaluated for pain score and, if placed in the range of moderate to severe headaches, they were candidates for receiving an injectable drug for controlling the headache and were therefore included in the study. Patients who were affected with or had a history of arrhythmias, ischemic heart disease, peptic ulcer, obsessive disorders, coagulation disorder, hypertension, inflammatory bowel disease, renal failure, liver failure, and sleep disorders, as well as pregnant women were excluded. Participants were selected using convenience sampling method. Patients who presented to the Shohadaye Tajrish Hospital's ED received ketorolac and patients who presented to Sina Hospital's ED received metoclopramide +

dexamethasone combination therapy. With a confidence interval level of 95% and a test power of 90%, considering $\alpha = 0.05$, and $\beta = 0.2$, the sample size in each group and the total sample size were 35 and 70 cases, respectively.

Intervention and Data gathering

The statistical population consisted of two groups, the first group received 60 mg of ketorolac and the second group received 8 mg of dexamethasone + 10 mg metoclopramide intravenously. Patients' pain was measured and recorded on arrival based on the visual analogue scale (VAS). Then, patients were treated with 8 mg dexamethasone + 10 mg metoclopramide or ketorolac depending on which hospital they were admitted to. In case of any complications such as tachycardia, hypertension, nausea, vomiting, injection site pain, itching, irritability or restlessness, drug injection was discontinued. After drug administration, pain intensity was measured again after 1 and 2 hours. A reduction of more than 3 points in VAS was considered as an appropriate response to treatment. There was no limitation for performing diagnostic evaluations due to prescribing drug. Moreover, if the patient's pain was not relieved by these drugs, a second-line drug (opioid) would be used for patients as rescue medicine.

Statistical analysis

Patient's demographic data and the previously mentioned variables were imported to IBM®-SPSS®-Statistics-V22.0 software for further analysis. Descriptive statistics including mean, frequency, percentage, and standard deviation (SD) were used to characterize the study population. The two groups were compared with t-test and ANOVA. Depending on the type of response, and the results of the normality test, the statistical tests of variance analysis and independent t-tests were used. In each treatment group, the mean pain scores were compared at different times with paired t-test and Bonferroni correction for multiple comparisons. P-value less than 0.05 was considered significant.

RESULTS

Baseline characteristics

Overall, 86 patients were enrolled, and 50 cases were male (58.1%). Their mean age was 37.6 ± 10.3 years with range of 19-77 years. Of the participants, 35 (40.7%) were in the group treated with ketorolac and 51 (59.3%) were treated with dexamethasone + metoclopramide. The mean and standard deviation of the age was 36.7 ± 10.1 years in the patients treated with ketorolac and 38.3 ± 10.5 years in the patients treated with

combination therapy of metoclopramide-dexamethasone ($p=0.49$). **Error! Reference source not found.** shows the age distribution of the two groups. In the beginning, the severity of perceived pain was 8.3 ± 1.6 in the ketorolac group, and 8.4 ± 3.1 in the combined treatment with dexamethasone + metoclopramide group. At this time, there was no significant difference in pain intensity between the two groups ($p = 0.78$).

Assessed pain intensity

Error! Reference source not found. shows the pain intensity of the two groups during the study period. One hour after medication administration, the reported pain intensity was 4.7 ± 2.0 in the ketorolac group, which decreased significantly more than that in the dexamethasone and metoclopramide group (6.2 ± 2.3). In other words, the pain reported at the first hour after drug administration in the ketorolac group was less than that in the dexamethasone + metoclopramide group ($p = 0.003$). Two hours later, the pain score was 3.4 ± 1.2 in the patients in the ketorolac group and 2.9 ± 1.3 in the dexamethasone + metoclopramide group, with no statistically significant difference between them ($p = 0.40$).

The treatment success rate

In this study, treatment success was defined as a reduction of at least 3 points in pain severity in comparison to the time of onset. Accordingly,

treatment success at the first hour after administration of drugs was 74.3% in the ketorolac group and 39.2% in the dexamethasone + metoclopramide group. At the second hour, treatment success rate was 85.7% in ketorolac group and 84.3% in the dexamethasone + metoclopramide group. It is worth noting that the pain score in 5 patients (14.3%) from the ketorolac group, and 8 patients (15.7%) from the dexamethasone + metoclopramide group had decreased less than 3 points after 2 hours.

DISCUSSION

This study assessed and compared the success rate of IV combination therapy using metoclopramide + dexamethasone with that of ketorolac therapy in acute migraine headaches. Although the pain response to the IV ketorolac was better one hour after treatment, finally, there was no significant difference in treatment success between the two therapies in the EDs.

A systematic review study supplied a modified classification of evidence for pharmacological therapies for acute migraine treatment, and showed that both ketorolac and metoclopramide are level B and probably effective for acute migraine (supported by 1 Class I study or 2 Class II studies), and that steroids are level C and possibly effective for acute migraine (supported by 1 Class II study or 2 Class III studies). Based on this systematic review, both metoclopramide and ketorolac have identical therapeutic effects (8).

A meta-analysis and systematic review study investigated the effect of adjunctive dexamethasone along with standard treatment of migraine, and demonstrated that combination of dexamethasone with standard therapy for migraine caused a reduction in the rate of patients with moderate or severe headache 24 to 72 hours after ED evaluation (RR = 0.87, 95% CI = 0.80 to 0.95; absolute risk reduction = 9.7%), publication and selection bias occur in these types of studies and are known limitations (9). A randomized clinical trial study compared intravenous dexamethasone and placebo as adjunctive therapies in decreasing the recurrence rate of acute migraine headache. Overall, 115 patients were included in the study, and 16 patients were missed to follow-up. On the 3rd day of follow-up, 35% (95% CI 24%-48%) of the dexamethasone group and 45% (95% CI 31%-60%) of the placebo group had recurrence of headache ($p=0.68$). This study showed that dexamethasone does not decrease the recurrence of headache as an adjunctive therapy (10). A few randomized clinical trials

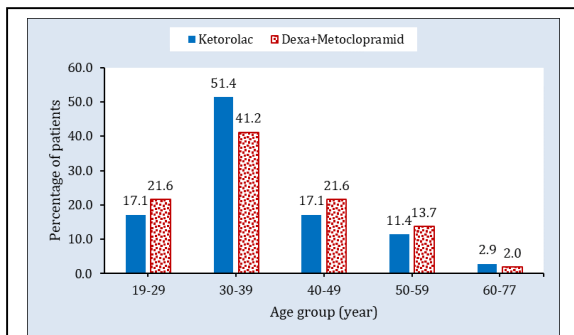


Figure 1: Age distribution of the patients in the two groups.

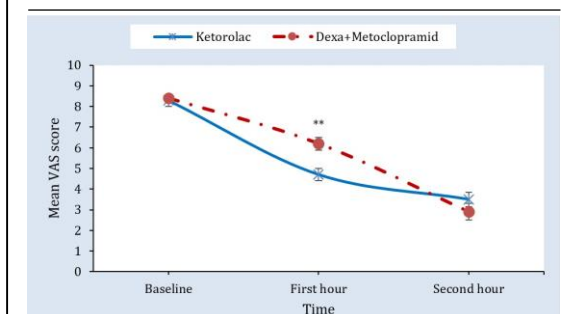


Figure 2: The pain intensity of the two groups throughout the study period.

demonstrated that metoclopramide has a significant therapeutic efficacy in acute migraine headache treatment. Among limitations of these studies are their sample size, failure to report inclusion and exclusion criteria, and failure to report adverse effects (11-13). A randomized double-blind clinical trial compared metoclopramide with sumatriptan in ED. At the second hour of treatment, pain-free rates were 59% in the metoclopramide arm and 35% in the sumatriptan arm (95% CI for difference of 24%: 2 to 46%). Finally, this study expressed that metoclopramide may be an acceptable therapy for acute migraine headache in ED (11). Another study compared combination therapy of metoclopramide + diphenhydramine with ketorolac and demonstrated that parenteral metoclopramide + diphenhydramine is more effective than ketorolac for acute migraine (14). In another study, Friedman et al. performed a randomized trial and showed that metoclopramide is more efficient than ketorolac or valproate sodium (15). A randomized double-blind dose-finding clinical study compared different dosages of metoclopramide for treating acute migraine. In this study, treatment with 10, 20, or 40 mg of metoclopramide was randomly assigned to patients and pain intensity was compared among the groups. An hour later, pain had improved by a mean of 4.7 numeric rating scale points in those who had received 10 mg (95% confidence interval [CI] 4.2 to 5.2 points); those who received 20 mg had improved by 4.9 points (95% CI 4.4 to 5.4 points), and those who received 40 mg had improved by 5.3 points (95% CI 4.8 to 5.9 points). Finally, the study showed that 20 and 40 mg of metoclopramide had no significant differences with 10 mg dosage (16). A meta-analysis and systematic review recommend using dexamethasone as a useful therapy for preventing headache recurrence and a safe adjunctive therapy to standard treatment for management of acute migraine headache in ED (17). Similarly, a meta-analysis of randomized clinical trials stated that adjunctive parenteral dexamethasone is associated with relief of headache recurrence in acute migraine (18). A study compared the efficacy of combined therapy of metoclopramide plus dexamethasone with magnesium sulfate. In this study, 70 patients with complaint of migraine headache were assessed in two groups. Those who received combination therapy had a reduction in pain intensity from 8 to 7.4 (20 minutes) ($p=0.36$), to 6.0 (1 hour), and 2.5 (2 hours) ($p<0.0001$). Additionally, those taking magnesium sulfate experienced pain reduction from 8 to 5.2

(20 minutes), 2.3 (1 hour), and 1.3 (2 hours) ($p<0.0001$). The study demonstrated that magnesium sulfate is more useful than combined therapy with metoclopramide and dexamethasone for acute migraine (19). Based on existing literature, it appears that metoclopramide and ketorolac have identical therapeutic effects in acute migraine headache, and that dexamethasone has a possible effect on decreasing the recurrence of headache. Studies on combined metoclopramide + dexamethasone therapy in acute migraine are few and further investigation is needed in this area.

Limitations

The first limitation, frequently seen in quasi-experimental studies, is the lack of random allocation to test groups. This limitation leads to non-equivalent test groups and consequently reduces the generalizability of the results. Previous factors and other influential factors are not taken into account because variables are not controlled in quasi-experimental studies and their effects on treatment may be missed. Another limitation is the sampling; results obtained via convenience sampling cannot be generalized to the population, and have insufficient power in detecting differences among socio-demographic subgroups. In addition, patients were discharged from ED after pain relief and were not followed for recurrence or late side effects, and the recurrence of headache was not compared between the two groups. There was no standard regimen to compare the two types of therapy with. Additionally, adverse effects of the two therapies were not reported.

CONCLUSIONS

Based on the findings of this study, the pain reduction time was relatively shorter in the ketorolac group, but the final response was identical in the two groups.

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AUTHORS' CONTRIBUTION

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

CONFLICT OF INTEREST

None declared.

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REFERENCES

1. Charles A. Migraine. *N Engl J Med*. 2017;377(6):553-61.
2. Farhadi Z, Alidoost S, Behzadifar M, Mohammadibakhsh R, Khodadadi N, Sepehrian R, et al. The Prevalence of Migraine in Iran: A Systematic Review and Meta-Analysis. *Iran Red Crescent Med J*. 2016;18(10):e40061.
3. Zhang Y, Parikh A, Qian S. Migraine and stroke. *Stroke Vasc Neurol*. 2017;2(3):160-7.
4. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. *Springerplus*. 2016;5:637.
5. Marmura MJ, Silberstein SD, Schwedt TJ. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. *Headache*. 2015;55(1):3-20.
6. Phueanpinit P, Pongwecharak J, Sumanont S, Krska J, Jarernsiripornkul N. Physicians' communication of risks from non-steroidal anti-inflammatory drugs and attitude towards providing adverse drug reaction information to patients. *J Eval Clin Pract*. 2017 Dec;23(6):1387-94.
7. Orr SL, Friedman BW, Christie S, Minen MT, Bamford C, Kelley NE, et al. Management of Adults With Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies. *Headache*. 2016;56(6):911-40.
8. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
9. Singh A, Alter HJ, Zaia B. Does the Addition of Dexamethasone to Standard Therapy for Acute Migraine Headache Decrease the Incidence of Recurrent Headache for Patients Treated in the Emergency Department? A Meta-analysis and Systematic Review of the Literature. *Acad Emerg Med*. 2008;15(12):1223-33.
10. Donaldson D, Sundermann R, Jackson R, Bastani A. Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial. *Am J Emerg Med*. 2008;26(2):124-30.
11. Friedman BW, Corbo J, Lipton RB, Bijur PE, Esses D, Solorzano C, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology*. 2005;64(3):463-8.
12. Loder EW. Review: intravenous metoclopramide is better than placebo for reducing pain in acute migraine in the emergency department. *ACP J Club*. 2005;142(3):77.
13. 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.
14. Friedman BW, Adewunmi V, Campbell C, Solorzano C, Esses D, Bijur PE, 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.
15. Friedman BW, Garber L, Yoon A, Solorzano C, Wollowitz A, Esses D, et al. Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. *Neurology*. 2014;82(11):976-83.
16. Friedman BW, Mulvey L, Esses D, Solorzano C, Paternoster J, Lipton RB, et al. Metoclopramide for acute migraine: a dose-finding randomized clinical trial. *Ann Emerg Med*. 2011;57(5):475-82.e1.
17. Singh A, Alter HJ, Zaia B. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the emergency department? A meta-analysis and systematic review of the literature. *Acad Emerg Med*. 2008;15(12):1223-33.
18. Colman I, Friedman BW, Brown MD, Innes GD, Grafstein E, Roberts TE, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ*. 2008;336(7657):1359-61.
19. Shahrami A, Assarzaghan F, Hatamabadi HR, Asgarzadeh M, Sarehbandi B, Asgarzadeh S. Comparison of therapeutic effects of magnesium sulfate vs. dexamethasone/metoclopramide on alleviating acute migraine headache. *J Emerg Med*. 2015;48(1):69-76.