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ORIGINAL ARTICLE

Effectiveness of intravenous dexamethasone, metoclopramide, ketorolac, and chlorpromazine for pain relief and prevention of recurrence in the migraine headache: a prospective double-blind randomized clinical trial

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Abstract

Dexamethasone, metoclopramide, ketorolac, and chlorpromazine have been used for the treatment of migraine headache. However, the effectiveness of these drugs in pain relief and prevention of recurrence and their side effects have not been compared yet. This was a randomized, double-blind clinical trial. Subjects were randomized to four groups; each received one of the following drugs intravenously: dexamethasone 8 mg, ketorolac 30 mg, metoclopramide 10 mg, and chlorpromazine 25 mg. The severity of headache in the two groups was assessed at starting point, 1 h and 24 h after the administration of drug using the visual analogue scale (VAS) on a scale of 0 to 10. No significant difference was found in the severity of symptoms between the four study groups before treatment, 1 h, and 24 h after treatment. The effect of all mentioned drugs on acute migraine headache was statistically significant at 1 and 24 h post-treatment compared to baseline. No significant difference was detected in the number of unresponsive cases between the four groups. There was a trend toward higher effectiveness of dexamethasone in prevention of recurrence ($P = 0.05$). Side effects were more common in chlorpromazine and less common in the dexamethasone-treated patients ($P < 0.001$). The present clinical trial shows the effectiveness of dexamethasone in prevention of recurrence and low frequency of treatment side effects.

Keywords Migraine · Dexamethasone · Metoclopramide · Ketorolac · Chlorpromazine

Introduction

Migraine is regarded as a common disabling health problem with the prevalence of 6% among men and 15 to 17% among women [9]. Headache or migraine headache has comprised approximately 5% of referrals to emergency departments [11]. International Headache Society (HIS) has classified migraine into two major subtypes of "migraine without aura" and "migraine with aura." The former is described as idiopathic, recurrent headache episodes lasting 4–72 h. Typical features are unilateral location, pulsating nature, moderate or severe strength, worsening by normal physical activity and association with nausea, photophobia, and phonophobia. The latter is defined as an idiopathic, recurrent headache disease demonstrated with episodes of neurological symptoms clearly localizable to the cerebral cortex or brain stem, typically emerging progressively over 5–20 min and continuing less than 60 min. Headache, nausea, and/or photophobia frequently occur after neurological aura symptoms immediately or following a free interim of fewer than an hour [8]. A subset of migraineurs come to the emergency departments. Management of these patients is more challenging compared with those having a typical attack at home for many reasons.

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First, they have tried some drugs without satisfactory relief before being visited in the emergency room. Moreover, the severity of migraine increases with time [5]. Dopamine-receptor antagonists (such as chlorpromazine and metoclopramide), non-steroidal anti-inflammatory drugs (such as ketorolac), and corticosteroids (such as dexamethasone) are among the drugs being used in management of acute migraine in adults in the emergency department situations [5]. In the present clinical trial, we aimed at comparing the efficacy of these treatments in pain relief and prevention of migraine recurrence as well as their side effects in patients referred to the emergency ward.

Material and methods

The current clinical trial study was conducted in the emergency ward of Farshchian teaching hospital, Hamadan, Iran (IRCT registration number IRCT201611239014N133). The study protocol was approved by the ethical committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1394.641). Patients who were complaining of headaches were examined by neurologists, and those who met the IHS criteria for migraine were selected for the study. All patients had episodic migraine and did not take preventive therapies. Patients did not have repeated referrals to emergency department. Headache intensity was scored based on the visual pain analogue scale (VAS) on a scale of 0 to 10, and those with scores higher than 4 were included in the study. Patients were also assessed to rule out life-threatening causes of headache such as subarachnoid hemorrhage, meningitis, arterial dissection, or high intracranial pressure. Patients with any of the following conditions were excluded from the study: hypertension, renal failure, any cardiac or respiratory disease, hepatic failure, epilepsy, malignancy, acute inflammatory disease or infection, peptic ulcer, pregnancy, breastfeeding, neurological deficit, history of immune-suppressive drugs, ergotamine use in the previous 8 h, and anxiolytic use in the previous 4 h.

The appropriate sample size for the study was calculated using the following equation where $p1$ and $p0$ were the efficacy of chlorpromazine and metoclopramide in reducing migraine pain, respectively [10, 12]:

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}}\sqrt{\overline{p}\left(1-\overline{p}\right)} + Z_{1-\beta}\sqrt{p_0(1-p_0)+p_1(1-p_1)}\right]^2}{d^2} \cong 32$$

$$p = \frac{p_0+p_1}{2} \quad , \quad d = 0.3 \quad , \quad p_1 = 0.95 \quad , \quad p_0 = 0.7 \quad , \quad Z_{1-\beta} = 1.28 \quad , \quad Z_{1-\frac{\alpha}{2}} = 1.96$$

A total of 128 (4 × 32) patients were randomly divided into four groups; each received one of the following drugs intravenously: dexamethasone 8 mg, ketorolac 30 mg, metoclopramide 10 mg, and chlorpromazine 25 mg. All drugs were injected in 50 ml saline normal solution within 15 min intravenously. Variables evaluated in the study were headache intensity according to VAS criteria (before treatment, 1 h and 24 h after treatment), family history of migraine, age, and sex. Vital signs, nausea, vomiting, photophobia, and phonophobia were evaluated. Patients and the staff who recorded the signs and filled the questionnaires were not aware of the type of injection. Side effects were assessed at both time intervals after treatment. Patients were followed after discharge through telephone calling.

Data acquired from the study were analyzed in SPSS 18. Descriptive statistics (mean ± SD), analysis of variance, and repeated measures (repeated measurement) were reported. Pain severity was assessed using one-way analysis of variance (ANOVA) with post hoc comparison. Logistic regression model was used for the evaluation of the relationship between a categorical response variable and categorical or continuous predictor variables. P values less than 0.05 was considered significant.

Results

A total of 128 persons including 27 patients with aura (mean age ± SD, 37.81 ± 9.27) and 101 patients without aura (mean age ± SD, 36.56 ± 10.10) participated in the study. Mann-Whitney U test showed no significant difference in mean age of two groups ($P = 0.53$). Logistic regression model showed higher frequency of females in both groups of patients (female/male ratio = 22/5 and 81/20, respectively). No significant difference was found in sex ratio between two groups. A total of 53.1% of patients had family history of migraine with no significant difference between two groups as evaluated by logistic regression model. Tables 1, 2, and 3 show the frequencies of aura in each group of patients before treatment and 1 and 24 h after treatment, respectively. No significant difference was found in the frequency of aura between patients treated with any of mentioned drugs at baseline, 1 h, and 24 h after treatment.

The intensity of headache was evaluated in four study groups before treatment and in two mentioned intervals (1 and 24 h after treatment) (Table 4). Based on the results of Kruskal-Wallis H test, no significant difference was found in severity of symptoms between four groups in any time intervals.

Figure 1 shows the linear presentation of headache severity in four groups in three tile intervals.

Table 1 The frequencies of aura in each group of treated patients before treatment

		Aura		Total
		Yes	No	
Dexamethasone	Count	3	29	32
	%	9.4	90.6	100.0
Metoclopramide	Count	7	25	32
	%	21.88	78.12	100.0
Ketorolac	Count	6	26	32
	%	18.75	81.25	100.0
Chlorpromazine	Count	11	21	32
	%	34.4	65.6	100.0
Total	Count	27	101	128
	%	21.1	78.9	100.0

Table 3 The frequencies of aura in each group of treated patients 24 h after treatment

		Aura		Total
		Yes	No	
Dexamethasone	Count	0	32	32
	%	0.0	100.0	100.0
Metoclopramide	Count	1	31	32
	%	3.2	96.8	100.0
Ketorolac	Count	0	33	32
	%	0.0	100.0	100.0
Chlorpromazine	Count	0	32	32
	%	0.0	100.0	100.0
Total	Count	1	127	128
	%	0.8	99.2	100.0

The effect of all mentioned drugs on acute migraine headache was statistically significant at 1 and 24 h post-treatment compared to baseline ($P < 0.05$).

A total of 17 patients (including 8 patients in metoclopramide group, 5 patients in ketorolac group, and 2 patients in each of the other two groups) did not respond to the prescribed drugs. Chi-square test showed no significant difference between the four groups in response to treatment ($P = 0.07$). In total, 15 cases experienced recurrence of migraine after initial satisfactory response to the prescribed drug (Table 5). There was a trend toward lower rate of recurrence in the dexamethasone-treated patients and higher rate of recurrence in the metoclopramide-treated patients ($P = 0.05$).

Finally, we assessed the frequency of reported side effects in each group (Table 6). No serious adverse effects were reported in the four groups. Chi-square test showed significant differences between the four groups in frequencies of minor side effects in a way that dexamethasone and chlorpromazine had the lower and higher side effects, respectively ($X^2 = 22.55$, $Df = 3$, $P < 0.001$). The reported side effects were mood changes and insomnia for dexamethasone; dizziness, nausea, malaise, and insomnia for metoclopramide; upset stomach, dizziness, nausea, drowsiness for ketorolac; and dizziness, drowsiness, anxiety, dry mouth, blurred vision, and constipation for chlorpromazine.

Table 2 The frequencies of aura in each group of treated patients 1 h after treatment

		Aura		Total
		Yes	No	
Dexamethasone	Count	0	32	32
	%	0.0	100.0	100.0
Metoclopramide	Count	1	31	32
	%	3.2	96.8	100.0
Ketorolac	Count	0	32	32
	%	0.0	100.0	100.0
Chlorpromazine	Count	0	32	32
	%	0.0	100.0	100.0
Total	Count	1	127	128
	%	0.8	99.2	100.0

Discussion

Although several drugs have been suggested for treatment of migraine headache, the efficacy of these drugs has not been accurately investigated and compared. In the present clinical trial, we assessed effectiveness of four commonly prescribed drugs for control of pain in migraine headache in emergency settings. All drugs were effective in control of pain in both time intervals. We found no significant difference in severity of symptoms between four groups in any time intervals. However, there was a trend toward lower rate of recurrence in the dexamethasone-treated patients and higher rate of recurrence in the metoclopramide-treated patients. Moreover, dexamethasone and chlorpromazine had the lower and higher side effects, respectively. Based on the obtained results, dexamethasone is the preferred drug for control of pain and prevention of recurrence. Previous studies comparing the effects of sodium valproate and dexamethasone on migraine headache reported no significant difference between these drugs in control of headache especially in patients without aura [3, 6]. In the present clinical trial, we detected no difference between patients with and without aura in response to any drugs. Although the four mentioned drugs have not been compared in a single clinical trial yet, previous studies reported have compared some pairs of these drugs. For instance, a previous prospective randomized double-blind trial in patients with

Table 4 The intensity of headache in four study groups before treatment and in the two mentioned intervals (1 and 24 h after treatment)

Drug		Before treatment	1 h	24 h
Dexamethasone	Mean	8.69	4.72	.81
	SD	1.491	1.708	1.491
	Minimum	5	2	0
	Maximum	10	10	5
Metoclopramide	Mean	8.42	4.42	2.06
	SD	1.455	2.157	3.434
	Minimum	5	0	0
	Maximum	10	9	10
Ketorolac	Mean	8.76	3.76	1.03
	SD	1.393	1.969	1.960
	Minimum	5	0	0
	Maximum	10	8	7
Chlorpromazine	Mean	8.97	4.22	1.91
	SD	1.204	1.718	3.145
	Minimum	6	1	0
	Maximum	10	7	10
Total	Mean	8.71	4.27	1.45
	SD	1.387	1.906	2.647
	Minimum	5	0	0
	Maximum	10	10	10
P values based on Kruskal-Wallis *H* test		*P* = 0.485	*P* = 0.368	*P* = 0.386

SD standard deviation

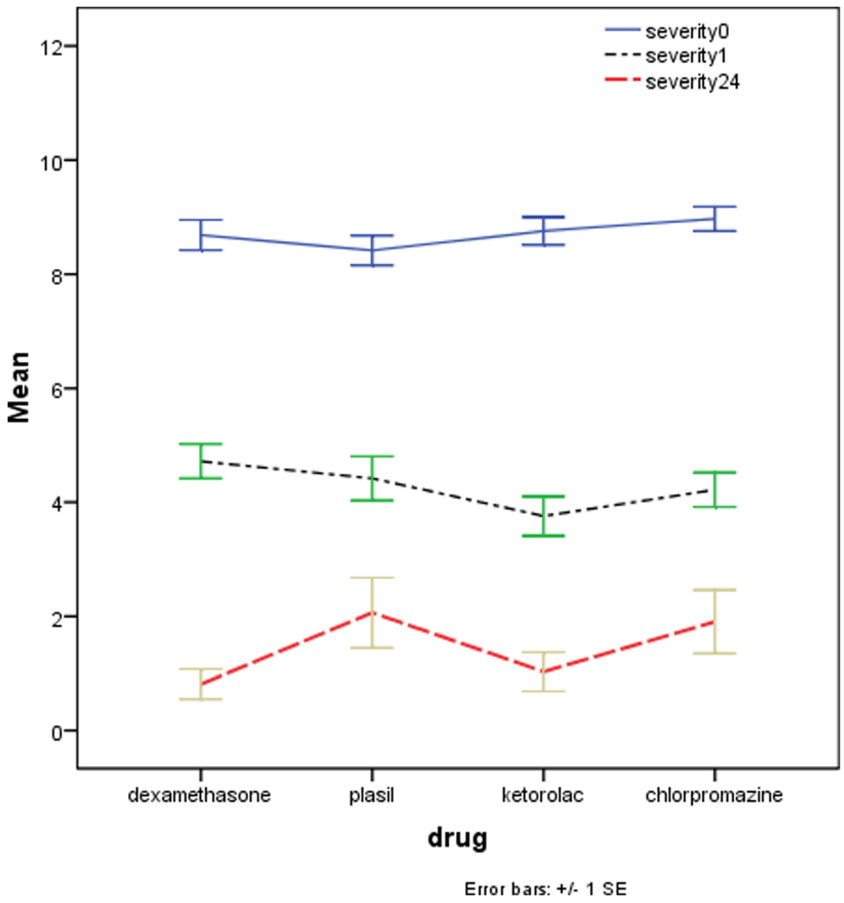

Fig. 1 The linear presentation of headache severity in four groups in three tile intervals

Table 5 The frequency of recurrence after initial response to the prescribed drug in each study group

	Recurrence		Total
	Yes	No	
Dexamethasone	0	32	32
Metoclopramide	6	26	32
Ketorolac	4	28	32
Chlorpromazine	5	27	32
Total	15	113	128

acute migraine has compared the effects of chlorpromazine and metoclopramide and reported effectiveness of both drugs in the management of acute migraine headache with similar minor side effect profiles [1]. Comparison of efficacy of chlorpromazine and ketorolac also revealed no differences between the mean pain scores or the mean change in pain scores [7]. However, another randomized clinical trial reported superiority of metoclopramide to ketorolac on numerous endpoints while less efficacy of valproate compared with either metoclopramide or ketorolac [4].

The results of our study regarding the lower rate of recurrence in the dexamethasone treated-patients are in line with the results of a meta-analysis which evaluated the efficacy of parenteral corticosteroids for the relief of acute severe migraine headache and avoidance of recurrence. The mentioned study reported effectiveness of dexamethasone compared with placebo in reducing recurrence rates. They also reported comparable side effect profiles between the dexamethasone and placebo groups [2]. Consequently, the lower recurrence rate and side effects of dexamethasone compared with the other three drugs along with its effectiveness in pain relief imply its superiority in management of acute migraine in emergency departments.

Finally, our study had a limitation. We considered the pain relief as the endpoint of efficacy and did not assess other symptoms such as nausea, vomiting, photophobia, phonophobia, or the capacity of patients to return to their daily activities. Future comprehensive studies are needed to evaluate all of these parameters.

Table 6 The frequency of reported side effects in each group

		Complication		Total
		Yes	No	
Dexamethasone	Count	6	26	32
	%	18.8	81.2	100.0
Metoclopramide	Count	10	22	32
	%	31.2	68.8	100.0
Ketorolac	Count	7	25	32
	%	21.8	78.2	100.0
Chlorpromazine	Count	22	10	32
	%	68.8	31.2	100.0
Total	Count	45	83	128
	%	35.2	64.8	100.0

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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