Российский журнал боли
2024, т. 22, № 2, с. 10-15
https://doi.org/10.17116/pain20242202110

Russian Journal of Pain
2024, vol. 22, no 2, pp. 10-15
https://doi.org/10.17116/pain20242202110

Оценка эффективности парентерального вальпроата натрия и дексаметазона для облегчения мигренозной головной боли. (Рандомизированное, двойное слепое контролируемое исследование)

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РЕЗЮМЕ

Введение. Лечение острой мигренозной головной боли в отделениях неотложной помощи остается сложной задачей. Целью этого исследования является уточнить эффективность вальпроата натрия при лечении острой мигренозной головной боли без ауры в отделении неотложной помощи.

Материалы и методы. 108 пациентов с умеренно-тяжелой мигренозной головной боли, набранные из отделения неотложной помощи, возрастом 18—60 лет и весом 50—85 кг были рандомно распределены на 2 группы: 1-я группа получала 1200 мг вальпроата натрия, остальные получали 8 мг дексаметазона, разведенного в 150 мл физиологического раствора, внутривенно в течение 10 минут. Первичный исход оценивал количество пациентов с головной болью до и через 1—2 часа после вмешательства, а также процент пациентов без головной боли через 2 и 24 часа после вмешательства.

Результаты. В экспериментальной группе количество головных болей сократилось до 2.33±1.74 через 1 час и 3.49±2.56 через 2 часа после начала лечения. В группе контроля уменьшение боли было зарегистрировано у 2.20±1.86 через 1 час и у 3.30±2.45 через 2 часа. Статистически значимого различия между группами отмечено не было. Вторичные исходы показали одинаковый процент пациентов, не нуждающихся в дополнительном обезболивании, в обеих группах.

Заключение. Эффективность внутривенного вальпроата натрия (1200 мг) значимо не отличалась от внутривенного дексаметазона (8 мг) в снижении острой мигренозной головной боли без ауры.

Ключевые слова: *вальпроат натрия, эффективность лечения, дексаметазон, мигренозная головная боль.*

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КАК ЦИТИРОВАТЬ:
Hassan Motamed, Meisam Moezi, Mohammadreza Dadkhah Tehrani. Parenteral sodium valproate and dexamethasone efficacy evaluation for alleviating migraine headache. (A randomized, controlled, double-blind study). *Российский журнал боли*. 2024;22(2):10–15. (In Russ.).
https://doi.org/10.17116/pain20242202110

Parenteral sodium valproate and dexamethasone efficacy evaluation for alleviating migraine headache. (A randomized, controlled, double-blind study)

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ABSTRACT

Introduction. Treating acute migraine headaches in emergency rooms remains a challenge. This study aimed to clarify sodium valproate's effectiveness in improving acute migraine headaches without aura in the emergency department

Material and methods. Selected from emergency room patients with moderate to severe migraine (VAS ≥4), 108 individuals aged 18—60 and weighing 50—85 kg were randomly assigned to two groups: one received 1200 mg sodium valproate, and the other received 8 mg dexamethasone intravenously in 150 ml of normal saline over 10 minutes. The primary outcome compared headache scores before and 1—2 hours after intervention, as well as the percentage of patients headache-free at 2 and 24 hours post-intervention.

Results. In the intervention group, headache scores reduced to 2.33±1.74 at 1 hour and 3.49±2.56 at 2 hours after intervention. In the control group, reductions were 2.20±1.86 at 1 hour and 3.30±2.45 at 2 hours. There was no statistically significant difference between the groups. Secondary outcomes showed similar percentages of patients not needing additional pain relief in both groups.

Conclusion. Intravenous sodium valproate (1200 mg) did not significantly differ in its effectiveness from intravenous dexamethasone (8 mg) in improving acute migraine headaches without aura.

Keywords: *sodium valproate, treatment efficacy, dexamethasone, migraine headache.*

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TO CITE THIS ARTICLE:
Hassan Motamed, Meisam Moezi, Mohammadreza Dadkhah Tehrani. Parenteral sodium valproate and dexamethasone efficacy evaluation for alleviating migraine headache. (A randomized, controlled, double-blind study). *Russian journal of pain*. 2024;22(2):10–15. (In Russ.).
https://doi.org/10.17116/pain20242202110

Introduction

Migraine headache is a chronic, high-prevalence, and sometimes debilitating neurovascular disorder that occurs in patients referred to the ED [1]. Migraine without aura is the most common type of migraine and includes about 80% of migraine cases [2]. Another type of migraine, namely classic migraine, occurs following a reversible aura and is less prevalent [3]. Generally, migraine attacks have an 18% prevalence in women and 6% in men [4]. Medications of choice for treating migraine headaches include nonsteroidal anti-inflammatory drugs (NSAIDs) [4], dopamine antagonists, triptans, dihydroergotamine (DHE), opioids, neuroleptic, and dexamethasone [5, 6]. Dexamethasone has been recommended for alleviation of attacks in ED and is effective with 8 to 24 mg doses in different studies [6, 7]. Sodium valproate is an anticonvulsant drug used in studies with 400 to 1200 mg doses on patients with varying degrees of migraine and shown to be effective and tolerable [2, 8, 10, 12, 13]. Sodium valproate increases GABA levels in the brain and affects the stimulation of dorsal raphe serotonergic cells, which play a role in headaches. Additionally, it reduces trigeminal central activity [9, 11]. The recommended dosage for the anticonvulsant effects of sodium valproate is 25 to 30 mg/kg daily, and up to 60mg/kg in some cases [11]. However, no optimal dosage is established for its effect on migraine. Different drug choices for acute migraine management may have different advantages or adverse consequences. Therefore, finding the best possible drug is an essential management cornerstone. Nonsteroidal anti-inflammatory drugs are one of the most widely used medications [17]. In this clinical trial, we aim to investigate and compare the effect of intravenous sodium valproate and dexamethasone on acute migraine headaches without aura. This study is registered at the Iranian Clinical Trial Registry with the allocated number allocated IRCT20180223038830N1.

Material and methods

Study Design

This is a double-blinded randomized trial conducted on patients referring to the triage of Golestan Hospital in Ahvaz, Iran, with acute moderate to severe migraine attacks with no aura. Patient enrollment was done based on the migraine diagnostic criteria in the 3rd edition of the International Classification of Headache Disorders (beta version) [14]. After that, the consent form of the patients was received.

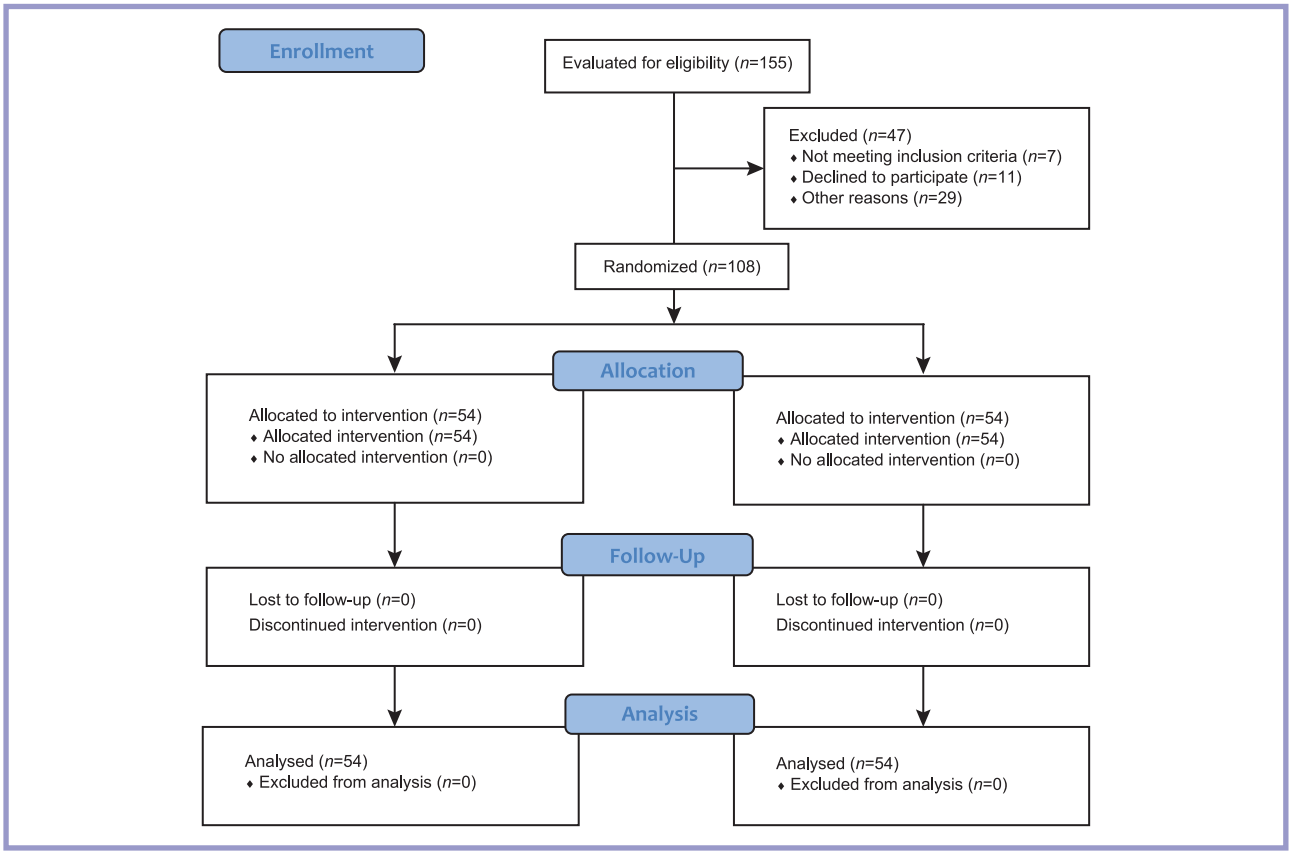

Fig. 1. **CONSORT flow diagram of the patients' enrollment.**

Table 1. **Demographic characteristics of patients, their weight, duration of migraine, and the presence of nausea and vomiting in the dexamethasone and sodium valproate groups**

Variables	Dexamethasone, *n*=54	Sodium valproate, *n*=54	*P* value
Age, *Mean*±*SD*, years	34.44±7.03	34.06±8.27	>0.05
Female, *n* (%)	39 (72.2)	41 (75.9)	>0.05
Male, *n* (%)	15 (27.8)	13 (24.1)	>0.05
Weight, *Mean*±SD, kg	77.3±5.8	75.8±7.55	>0.05
Duration of migraine <1 year, *n* (%)	6 (11.1)	8 (14.8)	>0.05
Duration of migraine ⩾1 year, *n* (%)	48 (88.9)	46 (85.2)	>0.05
Presence of nausea & vomiting, *n* (%)	46 (85.2)	44 (81.5)	>0.05
Presence of photophobia & phonophobia, *n* (%)	46 (85.2)	43 (79.6)	>0.05

Table 2. **Mean VAS score in the first and second hours after intervention**

Group	Baseline	First hour	Second hour	*P* value
Dexamethasone	8.34±0.985	6.139±2.387	5.037±2.988	<0.05
Sodium valproate	8.08±1.16	5.750±2.218	4.593±2.920	<0.05
P value	>0.05	>0.05	>0.05	—

Table 3. **Mean decrease in VAS score in the first and second hours after intervention**

Group	First hour	Second hour	*P* value
Dexamethasone	2.205±1.861	3.307±2.450	<0.05
Sodium valproate	2.338±1.743	3.496±2.567	<0.05
P value	>0.05	>0.05	—

Participants

Inclusion criteria were a history of migraine without aura for more than 6 months, aged between 18 and 60 years, moderate to severe headache (VAS score equal or more than 4), and body weight between 50 and 85 kg. Exclusion criteria were any systemic diseases (cardiovascular, pulmonary, neurological, metabolic, digestive, hepatic, renal, rheumatologic, malignancies, and acute infectious diseases), systolic blood pressure <90 mm Hg or over 160 mm Hg, use of injectable analgesics in the last 4 hours, use of ergotamine or triptans in the last 24 hours, use of mono amino oxidase (MAO) inhibitors drugs, anticonvulsants, tricyclic antidepressants, use of antiplatelet and anticoagulant drugs, and hypersensitivity to dexamethasone or sodium valproate.

Sample size, randomization, and blinding

Based on the literature [7] and with the calculation of 5% first-type error and 80% power, the minimum number of the study population was 98. So, with a possible loss of 15% of the participants, the final sample size was 108 patients, who were further assigned to two groups of 54 patients **(fig. 1)**. Before starting the study and selecting the samples, a pharmacist had prepared the drugs in 108 boxes of the same shape and weight, into two groups: Group A with 54 boxes containing 1 ampoule of 8 mg dexamethasone (Alborz Drug Factory), and group B with 54 boxes containing three vials of Depakin 400 mg (Sanofi-Aventis France) equal to 1200 mg sodium valproate. All of the 54 boxes in group A and also in group B were coded by using balanced randomization numbers from 1 to 108. In our study, as participants entered the study, their demographic and descriptive characteristics were recorded by the questioning physician. After that, the participants signed the consent form, and finally, a code number from 1 to 108 was assigned to them, respectively. Then, the participants were directed to the place of receiving the medicines, based on the same code numbers of the drugs, under the supervision of the treating physician.

Interventions and Outcomes

In the drug injection part, the content of drug boxes (1200 mg sodium valproate for intervention group or 8 mg dexamethasone for control group) in normal saline (150 mL) were infused within 10 minutes. The treating physician recorded the severity of headache based on VAS score at 0.5, 1, and 2 hours after intervention, and also recorded associated symptoms and the presence of side effects. The pain relief criteria was no or mild pain (VAS ⩽3). As a primary outcome, pain VAS score of baselines, compared with the 1st and 2nd hours following intervention. As a secondary outcome, the patient's need to use rescue drugs for refractory headaches when the pain VAS score remained persistent or its changes were negligible up to 2 hours after the intervention was evaluated. Furthermore, the patients who did not need, any other painkiller until discharge after the intervention (sustain headache relief) were determined. If the patient needs rescue drugs for refractory headache, or the patient showed unwillingness to further continue to participate at any time, he or she was referred to the emergency department physician for further treatment. After 24 hours of discharge of patients, during a telephone call, asked them for recurrence and any use of drugs or presence of side effects. Finally, the patients who did not need, any other painkiller until 24 hours after the intervention (sustain headache freedom) were determined.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences. (SPSS) software. In the descriptive analysis, the standard deviation and mean were applied to derive percentages

Table 4. **Need for rescue drug after intervention in each group**

Characteristic	Total participants, *n*=108 (%)	Dexamethasone group, *n*=54 (%)	Sodium valproate group, *n*=54 (%)	*P* value
Need to use rescue drug after intervention[1]	63 (58.33)	33 (61.11)	30 (55.56)	>0.05
No need to use any painkiller up to discharge[2]	45 (41.66)	21 (38.89)	24 (44.44)	>0.05
No need to any painkiller until 24 hours after intervention[3]	11 (10.18)	5 (9.26)	6 (11.11)	>0.05
Presence of side effects	13 (12.03)	2 (3.70)	11 (20.37)	<0.05

Note. [1]When the pain VAS score was remained persistent or its changes were negligible, up to 2 hours after intervention. [2]Sustained relief of headache. [3]Sustained headache freedom.

Table 5. **Percentage of nausea, photophobia, and phonophobia associated with migraine headache**

Characteristic	Dexamethasone group, *n*=54 (%)	Sodium valproate group, *n*=54 (%)	*P* value
Presence of nausea & vomiting before intervention	46 (85.19)	44 (81.50)	>0.05
Presence of nausea & vomiting after intervention	8 (14.81)	10 (18.51)	>0.05
Improvement of nausea & vomiting	38 (70.37)	34 (62.96)	>0.05
P value	<0.05	<0.05	
Presence of photophobia & phonophobia before intervention	46 (85.19)	43 (79.63)	>0.05
Presence of photophobia & phonophobia after intervention	7 (12.96)	8 (14.81)	>0.05
Improvement of photophobia & phonophobia	39 (72.22)	35 (64.81)	>0.05
P value	<0.05	<0.05	—

and quantitative variables, and tables and graphs were used for qualitative variables. For analytical analysis of the data, first, the data normality was measured for normal data distribution, then parametric tests, and Kolmogorov-Smirnov test were applied. The Chi-square test was applied for qualitative and quantitative variables between groups. Analysis of variance was applied to determine the differences between the two arms regarding quantitative variables. Repeated measurement was employed to examine the changes in quantitative data in two time periods in each experimental group, and a significant level of 0.05 was considered for the results.

Results

The participants were 39 (72.2%) female and 15 (27.8%) male (mean age 34.44±7.03 years) in the dexamethasone group (the control group), and in the sodium valproate group (the intervention group) were 41 (75.9%) female, and 13 (24.1%) male (mean age 34.06±8.27 years). The mean body weight of patients was 77.30±5.80 kg in the control group and 75.80±7.55 kg in the intervention group. The two groups had no significant demographic differences and were similar (*P*>0.05). The associated symptoms (nausea or vomiting) were present in 46 (85.2%) and 44 (81.5%) patients in the control and intervention groups, respectively **(table 1)**.

Photophobia or phonophobia were present in 46 (85.2%) and 43 (79.6%) patients in the control and intervention groups, respectively. The mean pain VAS score, 1 and 2 hours after the intervention was, 6.139±2.387 and 5.037±2.988 in the dexamethasone group and 5.750±2.218 and 4.593±2.920 in the sodium valproate group, respectively **(table 2)**. In the dexamethasone group, there was a decrease in pain VAS score of 2.205±1.861 and 3.307±2.450 in 1 and 2 hours after the intervention, and in the sodium valproate group, a decrease in pain VAS score of 2.338±1.743 and 3.496±2.567 in 1 and 2 hours following the intervention. The pain VAS score showed a significant decrease from before the second hour of the intervention in each group separately (*F*=186.13, *P*<0.05).

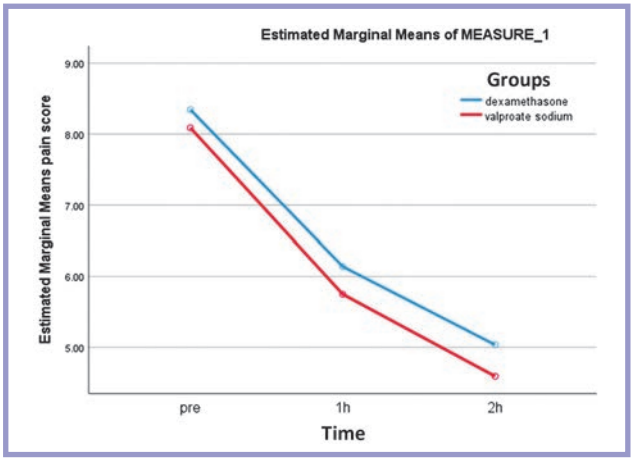

Fig. 2. **Estimated Marginal Means pain score demonstrating the reduction in both groups.**
The reduction in pain VAS scores was significant in both groups (*F*=186.13, *P*<0.05). However, there was no significant difference in headache score reduction between the two groups at admission and 1 or 2 hours after the intervention.

The headache score reduction between the two arms, at admission and in 1 and 2 hours after intervention, was (*t*= –0.384 and *P*>0.05) and (*t*= –0.391 and *P*>0.05), respectively, and insignificant **(table 3, fig. 2)**.

Out of the total 108 patients under study, 63 (58.3%) patients, including 33 (61.11%) patients in the dexamethasone group and 30 (55.56%) patients in the sodium valproate group, were administered the rescue drug within two hours after the

intervention, due to lack of any or negligible relief in headache score. No difference was detected between the two groups for need of rescue medication (Pearson's chi-square = 0.343, $P>0.05$) **(table 4)**. There was also no difference between the two groups for not needing rescue medication within two hours after intervention (Pearson chi-square = 0.343, $P>0.05$) **(see table 4)**. Only 11 (10.18%) of patients, including 5 (9.26%) patients in the dexamethasone group and 6 (11.11%) patients in the sodium valproate group, had sustained headache freedom and did not use any other painkillers until 24 hours after the intervention **(see table 4)**. A total of 13 (12.03%) people were affected by minor drug side effects. In the dexamethasone group, 2 (3.70%) patients experienced mild weakness, and in the sodium valproate group, 11 (20.37%) patients experienced the following symptoms: 5 (9.25%) patients had lethargy and weakness, 4 (7.40%) patients had nausea, and 2 (3.70%) patients reported epigastric pain. The difference in adverse effects between the two arms of study was statistically important ($P<0.05$). However, the side effects seen were minor and did not require medical treatment.

Discussion

Migraine is considered an independent factor in the development of chronic kidney disease, particularly in young men and individuals with comorbid diseases [18]. Proper drug selection is crucial to prevent such adverse effects. Managing migraines in the presence of renal and hepatic diseases poses a challenge because the biotransformation of pharmaceutical substances in these organs should be approached with extra caution. Renal and liver diseases can influence each other through the mediation of cytochrome 9450. NSAIDs have limitations for administration in severe renal and hepatic diseases when managing acute migraines. Triptans are suggested as an alternative in such cases. Additionally, Lasmiditan is a good choice for end-stage renal diseases, and Ubrogepant is suitable for severe hepatic diseases. Lasmiditan accelerates the recovery of acute kidney injury by inducing mitochondrial biogenesis. Dose adjustment for these drugs remains of high importance [19, 20].

Establishing a principle for managing acute migraines is challenging. According to our results, the therapeutic effect of sodium valproate and dexamethasone in reducing headache severity was significant in each group separately ($P<0.05$). However, there was no significant difference between the two groups ($P>0.05$) **(see fig. 2)**. In our study, 30 (55.56%) and 33 (61.11%) of patients in the sodium valproate and dexamethasone groups, respectively, required a rescue drug for their headaches because the VAS score did not change or only changed negligibly until 1 hour after the intervention **(see table 4)**. The rate of headache relief, defined as the percentage of patients whose headaches improved within 2 hours after the intervention and were then discharged, was 24 (44.44%) in the sodium valproate group and 21 (38.89%) in the dexamethasone group **(see table 4)**.

The percentage of patients with sustained freedom from headaches was 6 (11.11%) in the sodium valproate group and 5 (9.26%) in the dexamethasone group. Therefore, there was no significant difference between the two study arms ($P>0.05$) **(see table 4)**. In several studies, the improvement in headache due to sodium valproate was significant [12, 13, 15, 16]. In some studies, the role of sodium valproate versus dexamethasone in acute migraine headache was not significantly different [7]. In another study, sodium valproate was more effective than subcutaneous sumatriptan [7]. Yet in another study, headache relief was reported at a lower level with sodium valproate compared to ketorolac or metoclopramide [16]. Friedman et al. reported that the effect of 1000 mg sodium valproate in relieving acute migraine headache was less than 30 mg ketorolac or 10 mg metoclopramide. The percentage of patients with sustained freedom from headaches for sodium valproate was 4% (95% CI 1—9), for ketorolac 16% (95% CI 10—24), and for metoclopramide 11% (95% CI 5—17). The percentage of patients needing rescue medication was 69% (95% CI 60—78) for sodium valproate, 33% (95% CI 24—42) for metoclopramide, and 52% (95% CI 42—62) for ketorolac. This discrepancy in results appears to be related to hidden factors beyond variables such as the number of drugs, age, gender, and disease severity, including hereditary, cultural, social, and economic conditions of the patients, which make evaluation and interpretation challenging. However, in our study, despite using up to 1200 mg of sodium valproate and the lowest amount of dexamethasone (8 mg), the difference in the effect of these medications in reducing the severity of acute migraine without aura was not significant ($P>0.05$).

In our study, the rate of improvement in nausea and vomiting was 34 (62.96%) in the sodium valproate group and 38 (70.37%) in the dexamethasone group, and the percentage of improvement in the fear of light and sound was 35 (64.81%) in the sodium valproate group and 39 (72.22%) in the dexamethasone group. However, no significant differences were found in the improvement of associated symptoms of migraine headache between the two groups ($P>0.05$) **(table 5)**. Regarding side effects, we found that 13 out of 108 participants (12.03%) belonged to both groups, with 11 (20.37%) in the sodium valproate group and 2 (3.70%) in the dexamethasone group. It is important to note that the incidence of side effects was statistically significant between the two groups ($P<0.05$). It seems that the probability of side effects increases with the higher dose of sodium valproate, although they were mild **(see table 5)**. However, according to the results of our study, although there was a significant decrease in the pain VAS score with 1200 mg sodium valproate compared to 8 mg dexamethasone in acute migraine headaches without aura, no significant difference was detected between the two groups ($P>0.05$).

Conclusion

There is no statistically significant difference in the effectiveness of 1200 mg IV sodium valproate compared to 8 mg IV dexamethasone in improving acute migraine headaches without aura.

Limitations of the study

One of our limitations was the omission of evaluating psychological, cultural, social, and economic variables of patients, which appear to be influential and significant factors in migraine headache management. Furthermore, our study was conducted at the sole major neurology center in the city, possibly leading to a bias where most of our patients may have a treatment-resistant profile.

Authors' contribution

Conceptualization: MM. Methodology: MD. Validation: HM. Formal Analysis: HM. Investigation: MD. Resources: HM. Data Curation: MD. Writing—Original Draft Preparation: MD. Writing—Review and Editing: MD. Visualization: HM. Supervi-

sion: MM. Project Administration: MD. Funding Acquisition: Department of Emergency Medicine, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Ethical issues

The research adhered to the principles of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved the study (Approval ID: IR.AJUMS.REC.1396.718). The study was registered with the Iranian clinical trial registry (IRCT20180223038830N1, https://www.irct.ir). Written informed consent was obtained from all participants prior to their involvement in the study. It's important to note that this study was conducted as part of Mohammadreza Dadkhah Tehrani's emergency medicine residency thesis.

Funding/support. The project received funding from Ahvaz Jundishapur University of Medical Sciences under project number U-96119.

The authors declare no conflicts of interest.

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Поступила 08.11.2023
Received 08.11.2023
Принята к печати 16.03.2024
Accepted 16.03.2024