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Efficacy of Intravenous Paracetamol, Dexketoprofen, and Ibuprofen in Treating Headache Induced by Acute Migraine Attack

Şerife Örnek[1], Atakan Yılmaz[1], Alten Oskay[1], Aykut Kemancı[1], Mehmet Ulutürk[1], Yeşim Kınacı Çimen[2], Ezgi Demirözoğul[1], Murat Seyit[1], Mert Özen[1], İbrahim Türkçüer[1]

[1]Pamukkale University Faculty of Medicine, Department of Emergency Medicine, Denizli, Turkey
[2]Pamukkale University Faculty of Medicine, Department of Family Medicine, Denizli, Turkey

Abstract

Aim: Migraine is the most prevalent cause of admission to the emergency department (ED) with pain complaints. This study seeks to provide a comparative evaluation of the efficacy of intravenous paracetamol, dexketoprofen, and ibuprofen in treating headache induced by acute migraine attack.

Materials and Methods: Two hundred and seven volunteers with headache due to migraine attack were randomized into three groups. Group I was administered with intravenous paracetamol, Group II with intravenous dexketoprofen trometamol, and Group III with intravenous ibuprofen. A 100-mm visual analogue scale (VAS) score was used as an assessment scale to monitor dynamic changes in headaches during the 1-h observation of migraineurs.

Results: In Group I, the mean baseline VAS score was 79.65±13.87 and 11.83±14.37 at 60 min. In Group II, the mean baseline VAS score was 77.14±11.31 and 7.79±14.37 at 60 min. In Group III, the mean VAS score decreased from baseline 76.89±11.92 to 6.67±10.13 after 60 min. Considering the ΔVAS scores 30-min scores differed significantly between Group I and Group III (p=0.009).

Conclusion: IV paracetamol, dexketoprofen, and ibuprofen treatments did not differ significantly in acute migraine therapy. IV ibuprofen may be a first-line choice in EDs because of its immediate analgesic effect.

Keywords: Dexketoprofen, emergency department, ibuprofen, migraine, acetaminophen

Introduction

A large portion of the admissions to the emergency department (ED) with headache complaints are due to acute migraine attacks. The prevalence of migraine, one of the most common neurological disorders, is estimated to be around 15% in a one-year period across the world. Particularly in southeast Asia, the one-year prevalence reaches 25-30% (1). Recent research sets the prevalence of migraine at 11.7% in the USA, and gender-wise analysis reveals that its prevalence was 17.1% in females and 5.6% in males (2). In the Turkish context, its incidence was established as 2.38% (3), and its lifetime prevalence was 19.9% in men and 29.3% in women (4).

The treatment of headache induced by acute migraine attack in the ED is aimed at producing rapid, effective, and reliable analgesia with the least undesirable side effects, which does not trigger migraine and avoids the recurrence of pain after discharge. Although narcotic analgesics are likely to provide potent therapeutic effects and rapid onset of action, they can nevertheless present side effects, such as hypotension, nausea, vomiting, and dizziness (5). Therefore, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), such as dexketoprofen and ibuprofen, are frequently administered in the treatment of acute headache associated with migraine attack in EDs (5). Compared with NSAIDs, acetaminophen offers a wide margin of safety and a low incidence of side effects (6). The effectiveness of

Corresponding Author: İbrahim Türkçüer MD, Pamukkale University Faculty of Medicine, Department of Emergency Medicine, Denizli, Turkey
Phone: +90 258 296 63 11 **E-mail:** iturkcuer@yahoo.com **ORCID ID:** orcid.org/0000-0001-8342-4615

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acetaminophen in migraine headaches and its potential to be an alternative to other analgesics are crucial research topics that warrant further clinical investigation. Comparative studies are required to remove the question mark over which drug should be preferred (7).

Within this context, the present study seeks to provide a comparative evaluation of the efficacy of intravenous paracetamol, dexketoprofen, and ibuprofen in treating headache induced by acute migraine attack.

Materials and Methods

Study Design and Subjects

Our study was conducted at Pamukkale University Hospital Emergency Service between June 2018 and February 2020. This clinical trial was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (date: 29.05.2018, number: 11) and subsidized by the Pamukkale University Coordination Unit of Scientific Research Projects (2019TIPF006). Our study was registered and approved by the American clinical trial registry (NCT04372264 at https://clinicaltrials.gov). Our ED accomdates 120,000 annual patient encounters and during the study period a research assistant and/or faculty member managed this research 24 hours per day.

Among the patients admitted to the ED with the complaint of headache, those who met the 'International Classification of Headache Disorders' criteria for migraine without aura (8) and agreed to participate were recruited for our study after being evaluated in accordance with the inclusion and exclusion criteria.

Group I: Intravenous paracetamol (1000 mg) (Parol 1000 mg vial – Atabay Chemistry – İstanbul)

Group II: Intravenous Dexketoprofen Trometamol (50 mg) (Arveles 50 mg ampoule – Menarini – İstanbul)

Group III: Intravenous ibuprofen (400 mg) (Intrafen 400 mg vial – Gen – İstanbul)

After randomization, the drugs were diluted in 150 mL of physiological saline at the above-mentioned doses and administered as intravenous infusion (15 min). In addition, 10 mg metoclopramide in 150 cc physiological saline was administered intravenously to those with complaints of nausea as a 15-min slow infusion, concomitantly with the study drugs as standard care. Pain scores were assessed using the visual analog scale (VAS) at 0, 15, 30, and 60 min, and migraineurs were followed up in terms of vital signs and potential adverse effects. Each VAS score was marked on different forms. The migraineurs were followed up for 60 min in terms of efficacy, bioavailability, and complications of the drugs used in the study. The study was planned to terminate at 60 min, and patients with persisting pain were administered with a slow intravenous infusion of fentanyl 1 mcg/kg.

Data Collection

Our clinical trial recruited patients between the ages of 18 and 65 who presented to the ED with headache caused by acute migraine attack without aura, agreed to participate in the study, gave their informed consent, and matched the inclusion criteria. The specific considerations for patient selection are detailed in the following inclusion and exclusion criterion sections.

Inclusion Criteria:

- Suffering from headache due to acute migraine attack without aura,

- Being aged between 18-65,

- Providing written consent to participate in the study.

Exclusion Criteria:

- Taking analgesic drugs in the last 6 h,

- Taking ergotamine-derived drugs in the last 24 h,

- Being pregnant and during the lactation period,

- Being allergic to the study drugs,

- Hemodynamically unstable,

- Undergoing renal transplantation,

- Suffering from hepatic, renal, cardiac, and pulmonary insufficiency,

- Being a hypertensive patient whose blood pressure is not under control,

- A history of cerebrovascular disease,

- A history of ischemic heart disease or coronary spasm/prinzmetal angina,

- Having Wolff-Parkinson-White syndrome or arrhythmias accompanying accessory pathways,

- Suffering glucose 6 phosphate dehydrogenase (G6PD) deficiency,

- Having other systemic diseases,

- Having a VAS pain score of less than 50 mm,

- Illiterate and visually impaired,

- Patients with pathology on neurologic examination.

The study was planned to terminate in the event of any drug-related adverse effects observed during the study.

The relevant information of the eligible patients were noted in the study data form. A 100-mm VAS scale was used as the evaluation scale to track the dynamic changes in migraineurs' headaches. VAS markings in the evaluation form prepared for the study before and during the procedure were performed by the migraineurs themselves, regardless of the previous marking. The scores for acute migraine headache without aura were evaluated and recorded at 0, 15, 30, and 60 minutes.

Statistical Analysis

A power analysis was performed before the study, assuming that the difference between the study groups would have a small effect size (dz=0.3). Accordingly, when 59 participants were included in the study, 90% power would be achieved at 95% confidence interval. Thus, this study assigned 71 participants to the paracetamol group, 70 to the dexketoprofen group, and 66 to the ibuprofen group. A total of 207 migraineurs completed the study, and 95% power for VAS results was achieved for all three drugs at 95% confidence interval.

All statistical data were analyzed using Statistical Package for the Social Sciences v.22 package program. The continuous variables (age, pulse, respiratory rate, fever, VAS score, systolic and diastolic blood pressure) were presented as mean±standard deviation, whereas the categorical variables (gender, medication used, presence of nausea and rescue medication use) were presented as numbers and percentages. The conformity of the variables to the normal distribution was analyzed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk tests). In the case of normal distribution, an independent sample t-test was performed to evaluate the difference between categorical binary variables. Moreover, when the parametric test assumptions were met, the difference between categorical triple variables was analyzed using independent ANOVA. The categorical variables were compared using the chi-square test. The cases where the p value was below 0.05 were considered statistically significant.

Results

Of 207 migraineurs investigated within the scope of our study, 164 (79.2%) were women and 43 (20.8%) were men (Figure 1), with a mean age of 32.8 years. The medications used for migraine treatment included paracetamol given to 71 (34.3%) patients in Group I, dexketoprofen trometamol provided to 70 (33.8%) patients in Group II, and ibuprofen administered to 66 (31.9%) patients in Group III. Metoclopramide, on the other hand, was administered concomitantly to 158 (76.3%) migraineurs with nausea. Rescue therapy was performed for 6 (2.9%) migraineurs whose VAS scores were not reduced to below 50 mm. Four migraineurs in Group I required rescue therapy, whereas Groups II and III included one migraineur each who required this therapy. However, no significant difference was observed in the administration of rescue therapy between the three groups (p=0.238). Similarly, no significant difference was evident between the study groups with respect to gender, presence of nausea, and administration of rescue therapy (Table 1). No migraineurs in the study groups reported any side effects.

Clinical evaluation revealed a mean heart rate 81 beats per minute, respiratory rate 14 breaths per minute, and temperature of 36.8 °C with no significant difference noted between the groups in vital signs at baseline or any time point in the first hour after drug administration.

When the VAS scores were analyzed comparisons between groups yielded no significant difference in relation to baseline VAS scores. Also all three drugs were evaluated within themselves, a significant decrease was revealed at 15, 30, and 60 mins in comparison to the baseline score (Figure 2). The 15-min VAS score was 58.15±16.60 in the paracetamol group (I), 53.57±14.65 in the dexketoprofen trometamol group (II) and 50.61±16.16 in

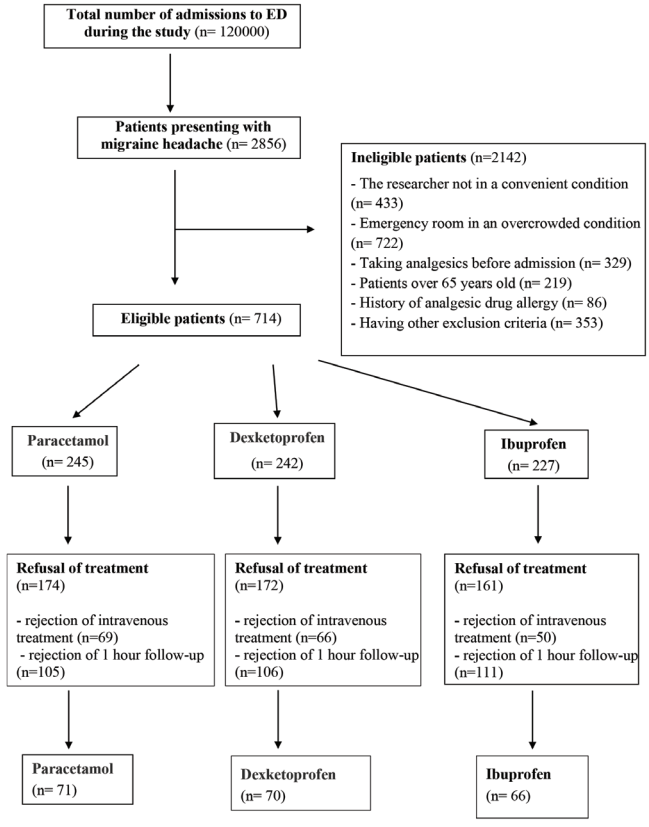

Figure 1. Flow chart
ED: Emergency department

Table 1. Demographic characteristics of the migraineurs and the study drugs					
	n (%)	**Group I paracetamol (n=71)**	**Group II dexketoprofen trometamol (n=70)**	**Group III ibuprofen (n=66)**	**p**
Gender	Female	60 (84.5%)	54 (77.1%)	50 (75.8%)	0.393
	Male	11 (15.5%)	16 (22.9%)	16 (24.2%)	
Presence of nausea	Yes	50 (70.4%)	58 (82.9%)	50 (75.8%)	0.219
	No	21 (29.6%)	12 (17.1%)	16 (24.2%)	
Rescue therapy	Yes	4 (5.6%)	1 (1.4%)	1 (1.5%)	0.238
	No	67 (94.4%)	69 (98.6%)	65 (98.5%)	
*Gender and presence of nausea presented as n (%). Pearson chi-square test was used. Significant values were highlighted in bold					

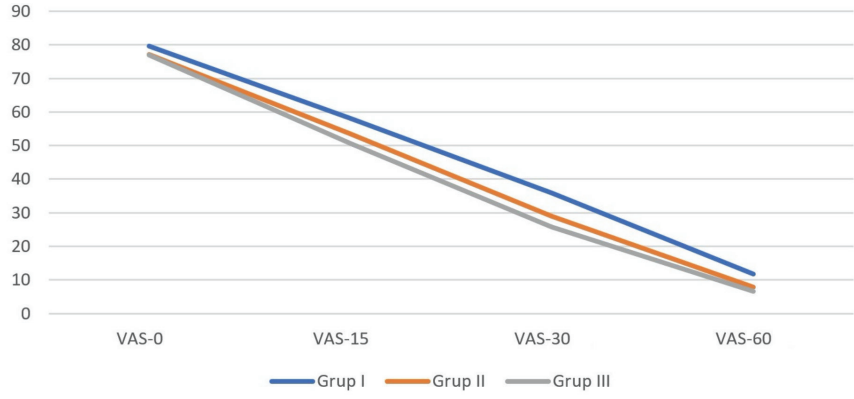

Figure 2. Time-dependent VAS score changes of the groups
VAS: Visual analogue score

the ibuprofen group (III). The 30-min VAS score was 35.92±17.69 in the Group (I), 28.93±16.13 in the dexketoprofen trometamol group II and 25.76±13.71 in the Group III. The 15- and 30-min VAS scores indicated significant differences between Group I and Group II, and between Group I and Group III (p=0.020) (p=0.001). Furthermore, statistical significance was noted between Group I, Group II, and Group III in the 60-min VAS scores (p=0.040). The ΔVAS 30-min score was 43.73±15.06 in the Group I, 48.21±13.88 in the Group II and 51.14±13.30 in the Group III. Considering the ΔVAS scores, 15- and 60-min VAS scores did not manifest a significant change between the groups (p>0.050), whereas 30-min scores differed significantly between Groups I, Group II and Group III (p=0.009) (Table 2).

No significant difference was detected between the patients in Group I and Group III given and not given metoclopramide concomitantly with the study drugs in terms of baseline, 15, 30, 60 min VAS, and ΔVAS scores (p>0.050). In Group II, no remarkable difference was found with respect to the baseline VAS, 30-min VAS, and ΔVAS scores between the migraineurs who were administered and not administered metoclopramide concomitantly with the study drug (p>0.050). The 15- and 60-min VAS scores of those not provided with metoclopramide were significantly lower (p=0.024; p=0.045). There was no significant change between 15- and 60-min ΔVAS scores (p>0.05) (Table 3). However, nausea symptoms were observed to disappear in all metoclopramide-given groups, and no add-on therapy was required.

Discussion

Our clinical trial on patients presenting with migraine-related acute headache without aura suggested that paracetamol, dexketoprofen, and ibuprofen significantly reduced VAS scores. The between-group analysis revealed that these drugs decreased VAS scores and produced an analgesic effect at a similar rate. Accordingly, IV forms of the aforementioned drugs administered to manage acute headaches can be an effective and safe treatment method. In addition, combined treatment with metoclopramide proved beneficial for treating nausea and vomiting accompanying migraine attacks.

In pain management, the migraineur should receive treatment as quickly as possible. Considering the treatment of migraine, the

Table 2. Distribution of the migraineurs' VAS scores across the groups

	Group I paracetamol (n=71)	Group II dexketoprofen trometamol (n=70)	Group III ibuprofen (n=66)	p
VAS 0 min	79.65±13.87	77.14±11.31	76.89±11.92	0.353
VAS 15 min	58.15±16.60	53.57±14.65	50.61±16.16	**0.020**
VAS 30 min	35.92±17.69	28.93±16.13	25.76±13.71	**0.001**
VAS 60 min	11.83±14.37	7.79±12.56	6.67±10.13	**0.040**
ΔVAS 15. min - 0 min	21.49±13.14	23.57±11.04	26.29±13.22	0.082
ΔVAS 30. min - 0 min	43.73±15.06	48.21±13.88	51.14±13.30	**0.009**
ΔVAS 60. min - 0 min	67.82±14.80	69.36±12.27	70.23±11.81	0.549

#VAS taken as mean±SD.
Differences were analyzed by ANOVA test.
Significant values were highlighted in bold. Absolute values were taken in ΔVAS scores.
SD: Standard deviation, VAS: Visual analogue scale

Table 3. Distribution of VAS scores of the patients in Group I (paracetamol + metoclopramide), Group II (dexketoprofen trometamol + metoclopramide), and Group III (ibuprofen + metoclopramide)

	Group I		p	Group II		p	Group III		p
	Paracetamol + metoclopramide (n=50)	Paracetamol only (n=21)		Dexketoprofen trometamol + metoclopramide (n=58)	Dexketoprofen trometamol only (n=12)		Ibuprofen + metoclopramide (n=50)	Ibuprofen only (n=16)	
VAS 0 min	80.90±13.65	76.67±14.26	0.243	78.28±11.10	71.67±11.15	0.065	77.30±12.30	75.63±10.94	0.628
VAS 15 min	58.78±17.94	56.64±13.17	0.628	55.34±14.17	45.0±14.46	**0.024**	51.60±17.65	47.50±10.0	0.381
VAS 30 min	37.60±18.80	31.90±14.36	0.218	30.09±15.91	23.33±16.70	0.069	26.40±14.68	23.75±10.25	0.505
VAS 60 min	13.0±15.56	9.05±10.91	0.294	8.71±13.20	3.33±7.79	**0.045**	7.20±11.07	5.0±6.33	0.328
ΔVAS 15 - 0 min	22.12±14.29	20.0±10.0	0.539	22.93±11.24	26.67±9.85	0.289	25.70±13.44	28.13±12.76	0.527
ΔVAS 30 - 0 min	43.30±15.21	44.76±15.04	0.712	48.19±13.60	48.33±15.86	0.974	43.30±15.21	44.76±15.04	0.712
ΔVAS 60 - 0 min	67.90±14.11	67.61±16.70	0.942	69.57±12.85	68.33±9.37	0.753	67.90±14.11	67.62±14.70	0.947

*VAS taken as mean±SD.
p obtained from the independent samples t-test.
Significant values were highlighted in bold.
SD: Standard deviation, VAS: Visual analogue scale

mean VAS score in the ibuprofen group was significantly lower than that in the paracetamol and dexketoprofen groups at 15 and 30 min and lower than that in the acetaminophen group at 60 min. Given the ΔVAS scores of all groups, ibuprofen was observed to provide a greater analgesic effect than acetaminophen at 30 min, although all drugs induced a similar decrease in the VAS scores at 60 min. These findings thus suggest that the analgesic effect of ibuprofen provides faster onset of action than other drugs. In parallel with our findings regarding ibuprofen, a recent comprehensive review established ibuprofen to be an effective and safe treatment for acute migraine headaches and a good option for the treatment of severe headaches because it produces relatively few side effects (9).

Turkcuer et al. (10) compared the effectiveness of IV paracetamol and dexketoprofen in acute migraine attacks, reporting that IV forms of these drugs achieved similar efficacy in pain control. Numerous clinical investigations have compared the administration of dexketoprofen trometamol alone or in combination with triptans with placebo and other analgesics, reporting that its administration alone or in combination proved effective in relieving migraine headaches (11-14).

Şafak et al. (15) compared the efficacy and safety of IV ibuprofen with IV dexketoprofen trometamol in 160 patients with migraine attack-related headaches. It was reported that a statistically significant difference was found in the VAS values at 30 min, and ibuprofen was more effective at the 30-min outcome, but no difference was found for the 60-min VAS values. Similar to this study, we found that VAS values were lower in the ibuprofen group than in the dexketoprofen trometamol group at 30 min, and ibuprofen was a faster agent. Contrary to the results of our study, Karacabey et al. (12) stated that pain relief with IV dexketoprofen was significantly higher and faster than that with ibuprofen.

An updated review study on the effectiveness and tolerability of acetaminophen alone or in combination with an antiemetic concluded that clinicians could resort to both applications to treat acute migraine attacks (16). In our study, there was no significant difference between the paracetamol group and the combination of acetaminophen and metoclopramide group in terms of VAS and ΔVAS scores and we thought that there is no superiority of the combination therapy of paracetamol with metoclopramide over acetaminophen alone.

Moore et al. (17) investigated the comparative efficacy of ibuprofen and paracetamol in migraineurs admitted to the ED with migraine headaches and documented the clinical superiority of ibuprofen across many acute and chronic pain conditions. Our study was found that ibuprofen had better VAS scores and acted faster at 30 min outcome when it compared to paracetamol.

Another aspect-deserving attention is that women experience migraine attacks three times more often than men (18,19). The incidence of migraine tends to increase in the female population along with the onset of puberty, and its prevalence among women of childbearing age far exceeds 15% (20). Although the reason for the gender-wise differences in migraine prevalence is not well established, some lines of evidence attribute this condition to lower pain resistance in women (21). Our study established that the proportion of female migraineurs was almost 80%, which broadly supports the work of other relevant studies.

The prevalence of migraine increases with age and shows a downward trend after the age of 40 years,with the mean age of patients at hospital admissions ranging between 35 and 40 years (22-24). As far as our results are concerned, the migraineurs were aged between 18 and 65 years,with the median value being 30 years and the mean age being 32.8 years, which is slightly lower than that reported in the literature. This situation might be because the ED of our tertiary hospital is located in a neighborhood where the inhabitants are predominantly young.

There is a growing academic interest in exploring the efficacy of metoclopramide in the treatment of acute migraine headaches. The mainstream view is that the co-administration of metoclopramide with existing drugs results in an efficacious treatment (25-27). In contrast to this view, other lines of evidence argue that metoclopramide does not achieve any clinical superiority over other treatments (28-30).

Metoclopramide is shown to produce a more potent analgesic effect at 15 min than ibuprofen and dexketoprofen, while ibuprofen proves less effective than dexketoprofen and metoclopramide (12). Dexketoprofen has also been shown to accelerate the pace of discharge of migraineurs from the ED (12). In a randomized double-blind controlled trial, Yavuz et al. (31) compared the effectiveness of IV metoclopramide versus dexketoprofen trometamol versus the combination of metoclopramide and dexketoprofen trometamol in a population of 150 patients. It was mentioned that no significant difference was found between the three treatment groups at the 15th min in terms of mean VAS scores, but the combination of metoclopramide and dexketoprofen trometamol was superior to both metoclopramide and dexketoprofen trometamol at the 30th min. Combination therapy was suggested for acute migraine pain in the ED. Similar to this study, a systematic review stated that the combination of metoclopramide and dexketoprofen gave better results than monotherapies in patients with migraine (32). Although we did not use metoclopramide for the treatment of migraine pain, contrary to the studies in existing literature, the combination therapy of dexketoprofen trometamol and metoclopramide had worse VAS scores than only dexketoprofen trometamol therapy in our study.

In our study, ibuprofen provided a faster onset of action than acetaminophen and dexketoprofen but exerted a similar effect at 60 min. The co-administration of the study drugs with metoclopramide did not contribute to any analgesic efficacy, except for the treatment of nausea and vomiting.

A systematic review probing the administration of ibuprofen alone and in combination with an antiemetic revealed that antiemetics showed minimal efficacy for treating migraine. However, the co-administration of ibuprofen with an antiemetic such as metoclopramide was observed to potentially provide better symptomatic relief from nausea and vomiting. It was also reported that ibuprofen could improve headache relief (33).

A randomized, double-blind, dose-ranging trial compared ibuprofen with both placebo and antiemetics on a population of 729 migraines. Given the clinical outcomes of the participants, ibuprofen reportedly reduced headache in about half of the patients and could be administered safely at a range of doses (34). In another double-blind, randomized and placebo controlled study, it was demonstrated that more pain relief within 2 hours after intravenous ibuprofen than placebo infusion (35).

Study Limitations

The results of the present study may have been affected by some limitations, including the absence of a comparison of the study drugs with placebo, inadequate follow-up period in terms of mobilization and functional capacity, and not assessing the recurrence of pain, re-admissions, and duration of ED stay. Another limitation can be cited as the exclusion of the migraineur using analgesics in the last six hours or an ergotamine-derivated

medication in the last 24 hours. The 60-min time span of the study might also be considered short.

Conclusion

Treatments performed with IV paracetamol, dexketoprofen, and ibuprofen generate similar analgesic effects, and these drugs can be considered safe for treating acute migraine without aura. Metoclopramide can be co-administered with the above-mentioned drugs in migraine therapy to prevent nausea. Because of its immediate analgesic effect, ibuprofen may be a first-line choice for treating headaches caused by acute migraine attacks in EDs.

Ethics

Ethics Committee Approval: This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (date: 29.05.2018, number: 11).

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., A.O., İ.T., Concept: Ş.Ö., A.Y., İ.T., Design: Ş.Ö., A.Y., İ.T., Data Collection or Processing: Ş.Ö., A.O., A.K., M.U., Y.K.Ç., E.D., M.S., M.Ö., İ.T., Analysis or Interpretation: Ş.Ö., A.Y., A.K., M.U., Y.K.Ç., İ.T., Literature Search: Ş.Ö., A.Y., A.O., A.K., M.U., E.D., M.S., M.Ö., İ.T., Writing: Ş.Ö., A.Y., A.O., A.K., M.U., Y.K.Ç., İ.T.

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