Signa Vitae

ORIGINAL RESEARCH

Oral paracetamol versus zolmitriptan to treat acute migraine attack in the emergency department

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Abstract

Background: Treatment provided in an emergency department is aimed at alleviating pain immediately with minimized adverse effects as well as warding off further migraine attacks. The primary aim of this article is to compare the effectiveness of oral paracetamol versus zolmitriptan in treating acute migraine attacks.

Methods: This prospective, randomized, and controlled study was carried out at a tertiary care hospital visited by 95,000 patients annually. The study recruited 200 participants who were randomized into two groups. One group received 1000 mg paracetamol while the other group received 2.5 mg zolmitriptan orally. Baseline pain scores were recorded using the Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS) at 15, 30 and at 60 min following administration of the study drugs. Patients requiring further treatment were provided fentanyl at a dosage of 1 μg/kg as a rescue therapy.

Results: A significant decrease was evident in VAS and NRS scores following the administration of the study drugs in both groups ($P < 0.001$). The change in VAS pain scores after 15, 30 and 60 min was calculated as 17.0 ± 13.9, 41.2 ± 16.3 and 61.2 ± 17.5 mm, respectively, in the paracetamol group and 14.2 ± 11.7, 39.2 ± 17.9 and 59.2 ± 19.3 mm, respectively, in the zolmitriptan group, which did not indicate significant differences ($P = 0.103$, $P = 0.425$, $P = 0.483$, respectively). Likewise, NRS pain scores showed a downward trend in line with VAS pain scores and did not yield a significant difference ($P = 0.422$). No significant difference concerning rescue therapy was noted between the two groups ($P = 0.596$).

Conclusion: Oral paracetamol and zolmitriptan prove to be similarly effective and have low incidence of acute side effects in treating acute migraine cases without aura.

Keywords

Emergency department; Migraine; Paracetamol; Zolmitriptan

1. Introduction

Roughly 3% of emergency department (ED) patients across the world present due to headache [1, 2]. Among patients admitted to ED for headache complaints, primary headaches are more prevalent than secondary ones. The most widely observed causes of primary headaches are migraine without aura, followed by other migraine types (migraine with aura, chronic migraine) and by less frequent tension type headaches [3]. Migraine is a chronic and sometimes progressive disease characterized by headache, recurrent attacks, and other related symptoms [4]. Generally, a unilateral and throbbing headache increasing with physical activity lasts between 4 and 72 hours, and headache is often accompanied by nausea and vomiting as well as sensitivity to light and sound [5]. The three approaches to migraine treatment involve avoiding triggers, bringing acute symptoms under control, and administering a pharmacological

prevention treatment [6]. Treatment provided in ED is aimed at alleviating pain immediately with minimized adverse effects as well as warding off further migraine attacks that might lead to re-admission to the ED [7].

Paracetamol is a widely used analgesic for acute pain with a low incidence of acute side effects in therapeutic doses. The systemic bioavailability of paracetamol is dose-dependent and ranges between 70% and 90% [8]. Paracetamol begins its pain relief effect 5-10 min after administration, achieving peak analgesic effect in 1 hour and usually lasting 4-6 hours [9].

Zolmitriptan is a synthetic tryptamine derivative and selective serotonin receptor agonist drug (5-HT1B/D) used in the treatment of migraine attacks with and without aura [9]. Zolmitriptan 2.5 mg oral tablets are the recommended dose for treatment in acute migraine attacks, allowing for pain relief within 1 hour of administration [10, 11]. Zolmitriptan tablet is reported to achieve an oral bioavailability of about 40% [12].

Zolmitriptan, a well-tolerated drug, starts its effect at 15 min, and reaches 75-80% of Tmax value within the first 60 min, providing rapid and effective analgesia which is sustained for 4 to 6 hours after dosing [13–16].

Our primary aim in this study was to reveal whether oral paracetamol was superior to zolmitriptan in ceasing migraine attacks in the ED, while the secondary aim was to compare the medications in terms of their adverse effects and requirement for rescue therapy.

2. Materials and methods

2.1 Study type and population

This prospective and randomized study was carried out between January 2016 and December 2016 at a tertiary care hospital visited by 95,000 patients annually. The study was approved by Pamukkale University Ethical Committee for Clinical Investigations, decision number 57051259-020 / 35149 dated June 11, 2015 and numbered 2015/11. This study was also enrolled in and endorsed by the American clinical trial registry (NCT03145467 at https://clinicaltrials.gov).

2.2 Participant selection

The study population consisted of patients aged 18-65 who presented to ED with headache complaints. Eligible patients were enrolled in the study after meeting the criteria of the International Classification of Headache Disorders for migraine without aura and giving their informed consent [17]. Patients with Visual Analog Scale (VAS) score > 50 mm and Numeric Rating Scale (NRS) score > 5 were included in the study. A physician evaluated the eligibility criteria for participating patients. Differential diagnosis for patients presenting to ED with non-traumatic headache was determined by assessing presence of nausea and vomiting, unilateral or bilateral pain, and the relationship between pain and effort.

Exclusion criteria were as follows: the most severe headache in patient's life, taking an analgesic in the previous 6 hours, pregnant or lactating, absence of informed consent, known allergy to the study drugs, hemodynamic instability, visual impairment, and pain character or severity different from previous migraine attacks. In addition, patients with renal transplants as well as those with liver, kidney, cardiac or pulmonary failure were excluded from the study.

2.3 Research protocol

The study groups and the administered drug doses were as follows:

Group 1: Paracetamol (500 mg) (Parol, Atabay, Turkey); 2 tablets orally (0.5 ₺ on average for two tablets in Turkey).

Group 2: Zolmitriptan (2.5 mg) (Zomig, AstraZeneca, Turkey); 1 tablet orally (8.5 ₺ on average for one tablet in Turkey).

This study followed a simple randomization method. First, an assistant blinded to the study calculated the randomization schedule on a computer. Then, eligible patients were assigned study numbers kept in sealed envelopes. A study nurse prepared the study drugs and administered them to the participants, who were screened in the monitoring unit of ED. A research assistant physician blinded to the study drugs followed up with participants and recorded their headache scores over the course of 60 min. In addition to the oral treatment, 10 mg metoclopramide in 150 cc saline was intravenously (IV) administered to patients with nausea or vomiting as a slow infusion for 15 min. At the end of 60 min, participants with VAS $\geq$ 50 mm were provided rescue therapy in the form of fentanyl at a dosage of 1 μg/kg.

2.4 Methods of measurement

We measured participants' pain levels along a 100-mm Visual Analogue Scale (VAS) ('no pain' = 0 and 'worst pain' = 100 mm) as well as a standard 11-point Numeric Rating Scale (NRS). Baseline pain scores were recorded at 15, 30 and 60 mins following administration of the study drug. Side effects reported by participants included allergic reaction, nausea, vomiting, dyspepsia, and others and were noted on the study form.

2.5 Outcome measures

The main outcome measures were the variations in VAS and NRS scores at 0, 15, 30 and 60 min, while the secondary outcome measures were the requirement for further drugs after 60 min and side effects.

2.6 Data analysis

Since a similar study involving these two drugs was not found in the published literature when we began our study, the results of studies with similar drugs were analyzed. A power analysis was performed for the effect size, which was determined hypothetically. The effect size was calculated with G*Power version 3.1.9.2 (Heinrich-Heine Universitat, Dusseldorf, Germany), considering the Cohen effect size (dz) value used for a paired-samples t-test. This is not a VAS- or NRS-specific coefficient, but rather a hypothetical coefficient intended to cover both.

Considering that the difference between the compared groups would have a small effect size (dz = 0.3), a power analysis was conducted at the beginning of the study. The analysis showed that including at least 90 participants per group would result in 80% power with a 95% confidence level. We thus included 100 participants for the paracetamol group and 100 participants for the zolmitriptan group. For the VAS results, we achieved 100% power with 95% confidence for both drugs (paracetamol dz = 4.02, zolmitriptan dz = 3.43). Statistical analyses were performed using SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY.) A Kolmogorov-Smirnov test was conducted to evaluate the normal distribution of data. Continuous variables were defined by the mean $\pm$ standard deviation. When parametric test assumptions were not met, a Mann-Whitney U test was used for between-group comparisons. For dependent group comparisons, a repeated measures ANOVA test was performed when parametric test assumptions were met, while a Friedman test was used for non-parametric test assumptions.
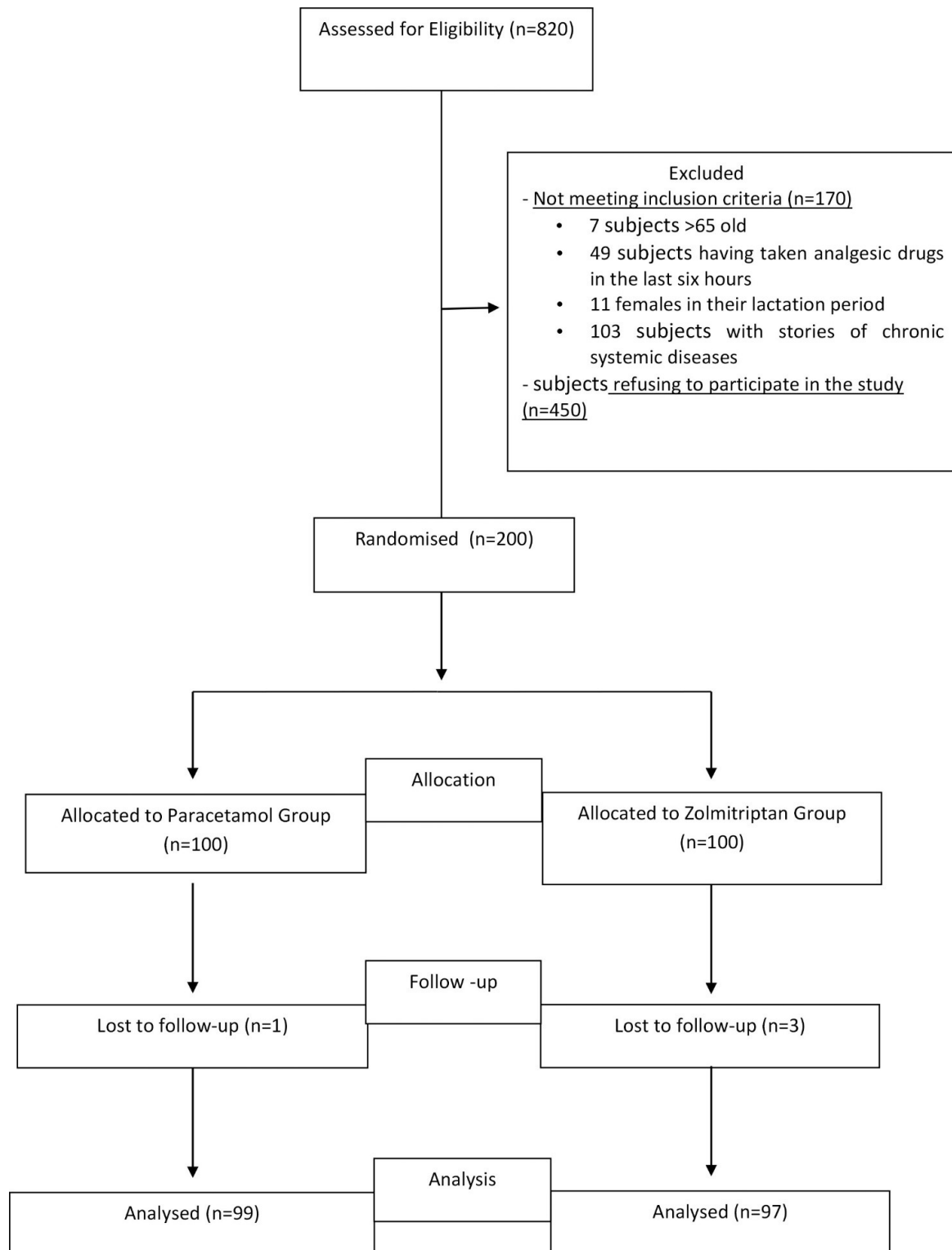
F I G U R E 1. Flow chart of the procedural course of the study.

T A B L E 1. Age and gender of participants.

	Paracetamol Group (n = 99)	Zolmitriptan Group (n = 97)	*P*
Female (n)	73 (73.7%)	70 (72.2%)	0.804*
Male (n)	26 (26.3%)	27 (27.8%)	
Age (Mean ± SD)	29.5 ± 10.3	32.2 ± 10.6	0.119**

P*: Obtained from the pearson chi-square test; P**: Obtained from the Mann-Whitney U test.
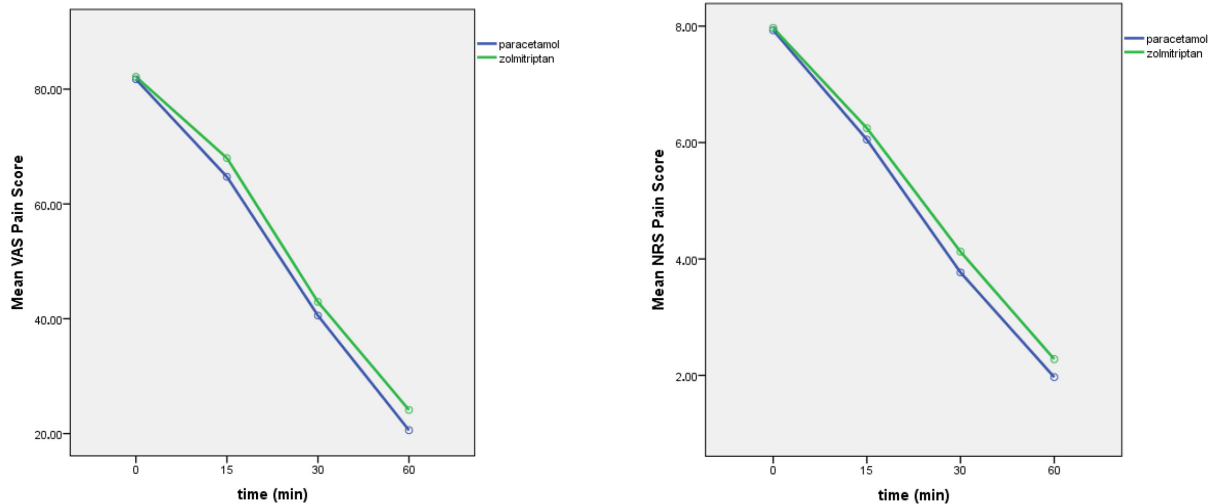
F I G U R E 2. VAS and NRS group scores in relation to time interval.

3. Results

Of 1405 patients presenting to the ED with primary headache complaints during the duration of the study, 820 were diagnosed with migraine without aura. For a variety of reasons, 170 patients were not eligible for the study, whereas 450 did not agree to take part. Therefore, a total of 200 participants (100 in the paracetamol group and 100 in the zolmitriptan group) were included in this study. However, one participant in the paracetamol group and three participants in the zolmitriptan group requested to withdraw from the study. Thus, the final analysis included 99 participants in the former group and 97 in the latter.

The majority of participants were female (73%, n = 143), with 73.7% (n = 73) in the paracetamol group and 72.2% (n = 70) in the zolmitriptan group (*P* = 0.804). The average age was 30.84 ± 10.5, specifically 29.5 ± 10.3 in the paracetamol group, and 32.2 ± 10.6 in the zolmitriptan group (*P* = 0.119). Table 1 presents the age and gender of participants. As indicated in Fig. 1, the full dosage was administered to all participants.

The VAS and NRS scores significantly decreased in both treatment groups over the course of the 60 min after the administration of the medications (*P* < 0.001) (Table 2). The change in VAS pain scores over the 60-min period was calculated as 61.2 ± 17.5 mm in the paracetamol group and 59.2 ± 19.3 mm in the zolmitriptan group (Fig. 2), which did not indicate a significant difference (*P* = 0.483). NRS pain scores showed a similar downward trend. The 60- min NRS pain score change was 5.9 ± 1.7 points in the paracetamol group, and 5.7 ± 2.0 points in the zolmitriptan group (Fig. 2), which did not yield a significant difference (*P* = 0.422). The differences in headache intensity between 0 to 15, 0 to 30, and 0 to 60 min were also considered separately for both VAS and NRS scores, but the differences between these scores were not statistically significant (Table 3).

Participants with symptoms of nausea or vomiting were administered 10 mg metoclopramide IV as a slow infusion. Metoclopramide treatment was provided as an add-on therapy to 37.4% (n = 37/99) of the paracetamol group and 30.9%

T A B L E 2. Variation of VAS and NRS pain score with time.

Pain Score	Paracetamol Mean ± SD	Zolmitriptan Mean ± SD	*P**
VAS-0	81.7 ± 9.8 bcd	82.1 ± 9.2 bcd	0.615
VAS-15	64.7 ± 14.8 acd	67.9 ± 13.0 acd	0.480
VAS-30	40.5 ± 16.3 abd	42.9 ± 18.7 abd	0.578
VAS-60	20.5 ± 17.5 abc	24.1 ± 19.5 abc	0.219
P**	< 0.0001	< 0.0001	
NRS-0	7.9 ± 1.2 bcd	7.9 ± 1.0 bcd	0.926
NRS-15	6.0 ± 1.5 acd	6.2 ± 1.4 acd	0.260
NRS-30	3.7 ± 1.7 abd	4.1 ± 1.8 abd	0.281
NRS-60	1.9 ± 1.7 abc	2.2 ± 2.0 abc	0.344
P**	< 0.0001	< 0.0001	

P* obtained from the Mann-Whitney U test. P** obtained from the Friedman test; a: Significant difference according to 0; b: Significant difference according to 15; c: Significant difference according to 30; d: Significant difference according to 60; All pairwise comparison P values were obtained from Friedman test with Bonferroni correction and all values P < 0.0001.

(n = 30/97) of the zolmitriptan group. Results indicated no significant difference between the two groups in number of participants receiving metoclopramide treatment (*P* = 0.341) (Table 4). When participants were categorized into four groups and compared as paracetamol-only (31.6%, n = 62/196), paracetamol + metoclopramide (18.9%, n = 37/196), zolmitriptan-only (34.2%, n = 67/196) and zolmitriptan + metoclopramide (15.3%, n = 30/196), no significant differences were noted between the groups in terms of decrease in VAS and NRS scores using the Greenhouse-Geisser test (*P* = 0.180 and *P* = 0.338, respectively) (Fig. 3). We also compared, independent of the study drugs, the VAS and NRS pain scores of participants who received metoclopramide (34.1%, n = 67) and those who
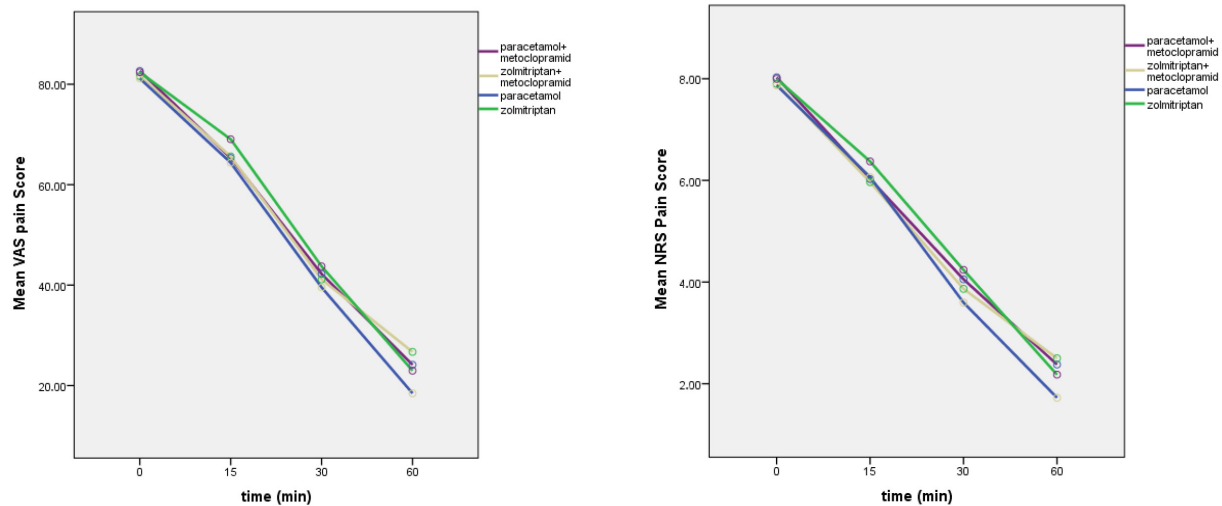
F I G U R E 3. VAS and NRS group scores with and without metoclopramide in relation to time interval.

T A B L E 3. Change of VAS and NRS scores at each time interval.

	Paracetamol	Zolmitriptan	P
Δ VAS 0-15 (mm)	17.0 ± 13.9	14.2 ± 11.7	0.103*
Δ VAS 0-30 (mm)	41.2 ± 16.3	39.2 ± 17.9	0.425**
Δ VAS 0-60 (mm)	61.2 ± 17.5	59.2 ± 19.3	0.483*
Δ NRS 0-15 (point)	1.9 ± 1.5	1.7 ± 1.4	0.363*
Δ NRS 0-30 (point)	4.2 ± 1.8	3.8 ± 1.9	0.211*
Δ NRS 0-60 (point)	5.9 ± 1.7	5.7 ± 2.0	0.422*

P*: Obtained from the Mann-Whitney U test; P**: Obtained from independent samples t-test.

did not (65.8%, n = 129). No significant difference was found between the two groups using the Mann-Whitney U test (VAS *P* = 0.884, NRS *P* = 0.775).

When the VAS pain score was ≥ 50 mm at 60 min, 19 (9.7%) of participants were provided rescue therapy. Of participants receiving rescue therapy, 8 (8.1%, n = 8/99) were in the paracetamol group and 11 (11.3%, n = 11/97) in the zolmitriptan group. No significant difference concerning rescue therapy was observed between the two groups (*P* = 0.596). Except for 4 participants (1 in the paracetamol group, 3 in the zolmitriptan group) who abandoned the study at their own request, no side effects were recorded in relation to the study drugs (Table 4).

4. Discussion

Today, migraine headaches as well as other intense headaches remain a frequent and major public health issue, most notably in women of reproductive age [18]. Migraine-induced headache is a common and debilitating disorder that emergency physicians frequently must treat. A wide range of therapies, including paracetamol, triptans, narcotic analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), are available to treat acute migraine attacks [10, 19]. Additionally, the treatment of migraine headaches in ED is important both to eliminate pain and return patients to their routine life im-

mediately. Paracetamol and zolmitriptan are two pain relievers with proven efficacy in migraine therapy, favorable oral bioavailability, low incidence of side effects, and peak analgesic efficacy within nearly one hour [8–10]. The current literature on acute migraine therapy without aura appears to lack a randomized, controlled trial comparing oral paracetamol and zolmitriptan directly, though a substantial body of research investigates drugs from the paracetamol and triptan groups. For these reasons, we selected oral paracetamol and zolmitriptan as the study drugs.

In this prospective and randomized study, we compared the effectiveness of oral paracetamol and zolmitriptan in patients admitted to the ED with acute migraine attacks without aura. When we compared the 15-, 30- and 60- min changes in the pain scales, we did not observe a significant difference between the two drugs. In relation to the VAS and NRS scores, at the end of 60 min a decrease of more than 70% was observed in both drug groups in comparison to baseline scores.

Given the results obtained, the effect size turned out to be substantially higher than planned prior to the study. Considering that 73% (n = 143) of our participants were women and the average age was 30.84 ± 10.5, the gender and age characteristics of our participants are in line with previous research, which validates the eligibility of our study population [4, 6].

As far as the current literature is concerned, ours can be considered as the first study conducted in the ED in which the effectiveness of oral paracetamol and zolmitriptan is compared in the treatment of acute migraine without aura. In accordance with our findings, it can be concluded that oral paracetamol and zolmitriptan might act as effective medications in treating acute migraine without aura, and a large body of research substantiates these results [20–22]. Nevertheless, our findings did not reveal the superiority of one drug relative to the other, which parallels findings reported by recent studies [19]. We further believe that the lack of a significant difference between groups in relation to rescue therapy (*P* = 0.596) confirms the similar effectiveness of both drugs.

In both groups, no participant reported any side effects within 60 min of taking the study drugs, demonstrating that

TABLE 4. Number of participants treated with metoclopramide and rescue therapy in study groups.

		Paracetamol (n = 99)	Zolmitriptan (n = 97)	*P**
Metoclopramide (n)	+	37	30	0.341
	-	62	67	
Rescue Therapy (n)	+	8	11	0.596
	-	91	86	

P*: Obtained from the Pearson chi-square test.

these drugs have low incidence of acute side effects in migraine treatment. Though similar research also supports this conclusion, our findings differ from those reported in other investigations in terms of incidence of side effects [23–25].

Participants who developed symptoms of nausea or vomiting were administered 10 mg metoclopramide IV as a slow infusion. A comparison of the groups with and without metoclopramide found no significant difference in terms of the reduction of headache. Although some research finds that metoclopramide may be effective alone in the treatment of migraine, its effectiveness in migraine therapy on its own is not within the scope of this study [10].

Another issue, while less important than treatment effectiveness and observed side effects, is treatment cost. The cost of paracetamol is 1/17th the cost of zolmitriptan, and both drugs have similar effects and low incidence of acute side effects. Moreover, some clinicians regard triptan-family drugs as second-line treatment after NSAIDs, yet the most likely reason for such a tendency is their relatively high cost in comparison to NSAIDs [26]. Therefore, cost might be a guiding factor for clinicians in choosing the most appropriate treatment.

The empirical results reported herein should be considered in light of some limitations. First, only patients presenting to the ED with acute migraine attacks without aura were included in this study, thus our results cannot be generalized to other migraine patients (for instance, migraine with aura or retinal migraine). Additionally, the 60- min interval may be considered short in some cases. We also did not measure some parameters, such as recurrent pain, readmission to the ED, and length of ED stay. Thus, further multi-center, randomized research is needed to increase external validity. Finally, although some research reports that metoclopramide can be effective on its own in migraine therapy, its effectiveness was not investigated within the scope of this study.

5. Conclusions

Both oral paracetamol and zolmitriptan prove to be similarly effective and have low incidence of acute side effects in treating acute migraine cases without aura.

AUTHOR CONTRIBUTIONS

Cuneyt Arikan and Atakan Yilmaz designed the study. Cuneyt Arikan, Ezgi Demirozogul and Atakan Yilmaz collected the data. Ibrahim Turkcuer, Mert Ozen and Murat Seyit analyzed the data. Cuneyt Arikan and Atakan Yilmaz analyzed the results and drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Pamukkale University Ethical Committee for Clinical Investigations, decision number 57051259-020 / 35149 dated June 11, 2015 and numbered 2015/11. This study was also enrolled in and endorsed by the American clinical trial registry (NCT03145467 at https://clinicaltrials.gov).

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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