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RESEARCH ARTICLE

Acute Treatment Comparison of Primary Headache Patients Admitted to Emergency Department: A Prospective Randomized Controlled Study

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HIGHLIGHTS

- This study aims to compare the efficacy of analgesic and non-analgesic treatment protocols in the acute treatment of adult primary headache patients admitted to the emergency department.
- Paracetamol, metoclopramide, and oxygen therapy were found similarly effective in primary headache treatments.
- We strongly suggest oxygen therapy as first-line therapy in primary headache, which has not statistically difference in efficacy, without known side effects and can be used repeatedly if require.

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ABSTRACT

Headaches are frequent and recurrent causes of emergency department visits. This study aims to compare the efficacy of analgesic and non-analgesic treatment protocols in the acute treatment of adult primary headache patients admitted to the emergency department. This study was a non-inferiority trial of oxygen therapy in primary headache, conducted as prospective cross-sectional research in the emergency department of a tertiary university hospital. The pain scales of the patients on admission and at the end of treatment were measured twice by Wong-Baker Faces Pain Rating Scale. The treatment effectiveness between the groups was compared statistically. A total of 215 patients were included in the study. The numbers of patients in groups were 68 patients (31.6%) in the group of intravenous metoclopramide HCl, 67 patients (31.2%) with nasal oxygen, and 80 patients (37.2%) with intravenous paracetamol treatment groups. Paracetamol, metoclopramide, and oxygen therapy were found similarly effective in primary headache treatments. Oxygen therapy should be recommended as the first-line treatment option, because, it has no known side effects, can be repeated if necessary and as effective as the paracetamol and metoclopramide.

Contents

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1. Introduction

T Headache is one of the most common problems encountered by physicians. Headache is a symptom that can accompany neurological diseases as well as systemic diseases. It negatively affects the quality of life of individuals. More than 90% of the population worldwide suffered at least once a headache complaint in their lives [1].

According to the International Headache Society (ICHD-3) 2018 guidelines, headaches are divided into three groups as primary headaches, secondary headaches, and Neuropathies & Facial Pains and other headaches group [2, 3]. Primary headaches have an organic cause that cannot be detected and is accompanied by symptoms like headache, nausea, vomiting and tearing. It usually starts at a young age and is repetitive. Mainly 90% of all headaches are primary headaches [3, 4].

Pain in the primary headache is usually an admission reason for emergency medicine. Non-specific and specific therapies are used to reduce the severity and frequency of attacks of primary headaches. Non-specific treatments include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), combined analgesics, narcotic analgesics, and antiemetics. In the specific treatment regimen, ergot alkaloids (serotonin receptor agonists) and triptans are mostly used [4, 5]. On the basis of the acute attack treatment of cluster headache, nasal or subcutaneous sumatriptan and high-flow (12-15 Lt/min.) 100% oxygen therapy constitute the main treatment regimen [2, 5–7]. In our study, we aimed to compare the efficacies of analgesic and non-analgesic treatments in the attack treatment of primary headache admitted to the emergency department.

2. Methods

2.1. Ethical Statement

This study complied with the followed Declaration of Helsinki. All patients provided written informed consent to participate in this study. In this study, approved by the research ethics review committee of the Atatürk University Clinical Research Ethics Committee (reference number B.30.2.ATA.0.01.00/215).

2.2. Study Design and Adjustment

This is a prospective cross-sectional study conducted at the Emergency Department (ED) of the tertiary university hospital, serving at least one million populations. Before conducting the study, necessary permissions were obtained from the clinical research ethics committee.

Among the patients who were admitted to the ED with the complaint of headache between June 1st and November 30th, 2018, patients diagnosed with primary headaches were included. Informed consent was obtained from all patients.

The patients who admitted to the ED with a diagnosis of primary headache according to ICHD-3, 2018 classification were included in the study and primary headache pre-diagnosis was made by the neurologist. Demographic characteristics, headache character, location, frequency, duration, severity, presence of accompanying findings and frequency of analgesics use were questioned. The patients' headache severity at the arrival was graded using the Wong-Baker Pain Scale (WBS). Randomized patients were treated with different treatment regimens. The headache severity of patients was re-evaluated according to the WBS scale 30 minutes after the treatments. The patients whose complaints had regressed were discharged from the ED with recommendations. As a salvage therapy for patients whose complaints did not regress, intravenous (IV) metamizole was administered. The patients whose headache did not disappear despite the salvage therapy were admitted to the neurology clinic for further examination and treatments.

2.3. Participant Selection

Primary headache patients age ≥ 18 years old were included in the study. Patients who have an allergy to treatment regimens, secondary headaches, pregnant, breastfeeding mothers, patients younger than 18 years and the patients who did not give informed consent were excluded from the study.

2.4. Measurement Methods

Before the treatment, the severity of the pain at arrival was determined by using the WBS scale. Thirty minutes after the treatment, patients were re-evaluated with the same scale. The success rates of the treatment regimens were detected by the differences between two scale rates and analyzed statistically.

2.5. Randomization

Using the rand () command from the Excel program, persons were assigned to three groups in a way to become 50/50/50, as being A between 0-0.33; B between 0.33-0.66; C between 0.66-1. After determining 50 patients, the randomization table is used to turn back to the beginning.

2.6. Treatment Regimens

In this study, two often applied metochloropramide and paracetamol treatment protocols of primary headaches were chosen to compare the efficacy of the oxygen therapy in the primary headache treatment, without determination of the subtypes of primary headache reasons. On account of the different application routes of the nasal oxygen and the other two intravenous treatment groups, blindness could not be performed in the treatments. In order to eliminate the bias caused by the treatment procedure, small amount of (100 mL) isotonic saline solution was administered intravenously along with the oxygen therapy to achieve the same route administration sensations in all groups. Before the

application of three treatment regimens, pain severities of patients were determined by WBS scale, and repeated 30 minutes after the treatments to detect the treatment efficacies. In case of the failure of the treatments after 30 minutes, salvage treatment procedures were applied to all three groups.

Three groups were randomized by the randomization table and later, the treatment regimens and salvage treatments were given in standard therapeutic doses. After preparing the randomization table, medications were given in treatment regimens as;

Group 1: 10 mg/2 mL metoclopramide HCl (Primperan, Biofarma Pharmaceutical Industry Co. Inc., Turkey) administered IV in 100 mL isotonic saline.

Group 2: 100 mL isotonic saline IV and nasal oxygen 10l/min.

Group 3: Paracetamol 10 mg/mL 100 mL (Perfalgam, Bristol-Myers Squibb Pharmaceuticals Ltd., UK) administered IV.

Salvage therapy: 1 g/2 mL metamizole sodium (Novalgin, Sanofi Aventis Pharmaceuticals Ltd., Turkey) administered IV in 100 mL isotonic saline.

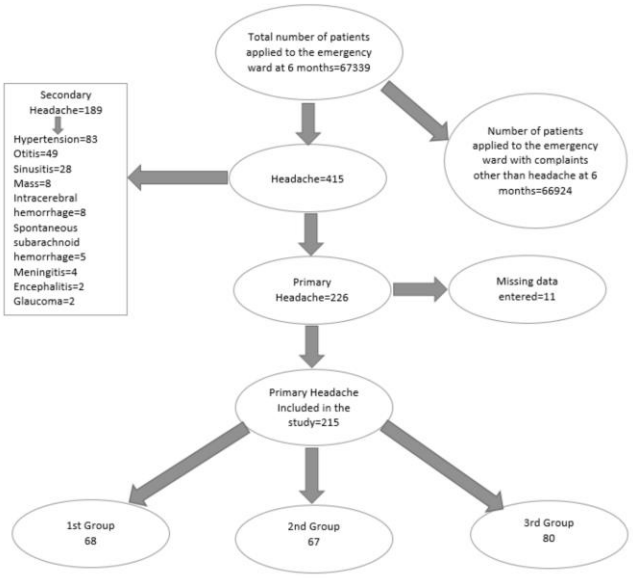

Figure 1 Patient Flow Chart

2.7. Data Analysis

To calculate the sample size, we studied the headache severity WBS scale in 3 groups with a 95% confidence level and 80% strength by using the NCSS PASS Sample Size Software program. In case of mean ± standard deviation is 4.5 ± 2 for Group 1, 5.5 ± 2 for group 2 and 6.6 ± 1.5 for group 3, the necessity of 50 patients was calculated to achieve significance in each group.

SPSS Statistics software program, version 25 (IBM Corporation, New York, NY, USA) was used for statistical analysis. The normal distribution of continuous variables was analyzed with the Shapiro-Wilk test. When comparing the two dependent groups, the Paired Samples t-test was used in the case that a normal distribution condition is provided, and the Wilcoxon test was used when it was not distributed normally. When comparing more than two independent groups and continuous variables, the ANOVA test was used in the case that a normal distribution condition is provided, and the Kruskal-Wallis test was used when it was not provided. The comparison between categorical variables was made with Chi-Square and Fisher's Exact test. The statistical significance level was accepted as $p<0.05$.

3. Results

In our study, we prospectively picked 226 headache patients admitted to our ED between June 1st and November 30th, 2018. Eleven patients were excluded from the study due to missing data (Figure 1).

Table 1 Demographic and Headache Characteristics of Patients

	N	**$\bar{x}$ ±SD**
Age	215	40.6±14.8
	N	%
Gender		
Female	124	57.7
Male	91	42.3
Comorbidities		
HT	12	5.6
CAD	3	1.4
DM	2	0.9
Hyperthyroidism	2	0.9
COPD	1	0.5
CRF	1	0.5
Breast Cancer	1	0.5
DM+HT	5	2.3
DM+HT+CAD	3	1.4
Asthma+HT	1	0.5
Arrhythmia + Hyperthyroidism	1	0.5
HT + CAD	1	0.5
HT + Hyperthyroidism	1	0.5
No	181	84.2
Analgesic Use History		
Once a month	62	28.8
Once a week	44	20.5
Two or more per week	23	10.7
No	86	40
Headache Type		
Migraine	116	54
Tension	84	39.1
Cluster	4	1.9
SUNCT	5	2.3
Stabbing	1	0.5
Cough	4	1.9
Sexual Activity	1	0.5
Total	215	100
Character of Pain		
Throbbing	101	47
Compressing	37	17.2
Drilling/Carving	13	6
Burning/Drilling	4	1.9
Stinging/Throbbing	8	3.7
Stabbing	4	1.9
Stabbing/Throbbing	3	1.4
Blunt	14	6.5
Blunt/Throbbing	13	6
Compressing/Throbbing	18	8.4
Duration of Pain		
4-72 hours	108	50.2
0.5 hours-7 days	18	8.4
15-180 minutes	34	15.8
2-30 minutes	14	6.5
5-240 seconds	1	0.5
1-10 seconds	1	0.5
1-30 seconds	8	3.7
5 minutes - 48 seconds	3	1.4
30-180 minutes	19	8.8

1 hour-10 day	9	4.2
Severity of Pain		
Mild/Moderate	46	21.4
Mild/Severe	13	6
Moderate/Severe	56	26
Severe	68	31.6
Extremely Severe	29	13.5
Different	3	1.4
Frequency of Pain		
Different	162	75.3
1-8/Day	16	7.4
5>/Day	7	3.3
3-200 Days	3	1.4
Related to Cough	4	1.9
Related to Exercise	2	0.9
More than 15/Month	8	3.7
Does Not Recur Regular	13	6
Location of Pain		
Frequently Nape/Forehead	69	32.1
Frequently Nape	31	14.4
Orbital/Suborbital	36	16.7
Orbital/Temporal	20	9.3
Back of the Head	24	11.2
Common	33	15.3
Nape/Common	1	0.5
Finding Accompanying to Headache		
Nausea/Vomiting	61	28.4
Loss of appetite/Nausea	36	16.7
Autonomic Symptoms	2	0.9
Conjunctival Injection and Tearing	10	4.7
Nausea/Vomiting/Loss of appetite	7	3.3
No	99	46
Lateralization Finding of Headache		
Bilateral	101	47
Unilateral	114	53

HT; Hypertension, CAD; Coronary Artery Disease, DM; Diabetes Mellitus, COPD; Chronic Obstructive Pulmonary Disease, CRF; Chronic Renal Failure, SUNCT; Short Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing

The percent of female patients in the study was 57.7% (n=124). The average age of men was 41 years, while the average age of women was 40.3. There was no significant difference between the study groups in terms of age and gender (p=0.11; p=0.34). Some of the patients (n=34) had comorbid diseases (15.8%). Among the chronic diseases, hypertension was the most common type with 5.6% (n=12). There was no history of analgesic use in 40% of the patients (n=86), whereas, 10.7% (n=23) had a history of two or more analgesic uses per week (Table 1).

According to ICHD-3, headache character, duration, severity, frequency, location, accompanying findings and lateralization of the pain of the patients were examined. the type of headache was migraine in 54% of the patients (n=116) and tension-type headache in 39,1% (n=84). The pain character was throbbing in 47% (n=101) of the patients. The pain duration was between 4-72 hours in 50.2% (n=108) of patients. In 46% of the patients (n=99), there were no accompanying symptoms, whereas, in 28.4% (n = 61) it was seen that nausea and vomiting accompanied the most frequently. When the severity of the headache of the patients was questioned, it was observed that 21.4% (n=46) of the patients had mild to moderate headaches, but the majority of patients defined severe headaches. When the side of the pain was questioned, 53% (n=114) showed unilateral pain (Table 1).

When the treatment effectiveness of migraine treatments was compared, the change in pain scores between 0-30th minutes score of WBS was found to be 4.6±2.2 in metoclopramide treatment; 4.4±2.9 in oxygen therapy group; and in the paracetamol group, this difference was found to be 5.2±2.3. The treatment efficacy of these three groups in migraine treatment was not statistically significant (p=0.43). The change in pain score between 0- 30th minutes score of WBS in the three types of treatments in tension type headache was 3.8±1.9 in metoclopramide treatment; 4.8±1.8 in oxygen therapy group; and in the paracetamol group, this difference was found to be 4.7±2.4. Similarly, the change in WBS scores of the tension-type headache treatment groups was not statistically significant (p=0.17). When we assess WBS pain score changes in three treatment groups without taking into consideration the primary headache classification, WBS score changes of 0-30th minutes were found to be 4.2±2.1 in metoclopramide treatment group; 4.5±2.5 in oxygen therapy group; and in the paracetamol group, this difference was found to be 4.8±2.3. This results show that the change in WBS pain scores in treatment groups was not statistically significant (p=0.37). The treatment efficacies of the given three treatment protocols were statistically seen not to be affected by the age (p=0.11) and gender (female and male, respectively, p=0.79; p=0.39) of the patients (Table 2).

Table 2 Mean of Primary Headache WBS 0-30 Minutes Difference Score ± SD; Median (min-max)

	Metoclopramide +100 cc SF	Oxygen +100 cc SF	Paracetamol	p-value
Headache Type				
Migraine	4.6±2.2;4 (0-8)	4.4±2.9;4 (0-10)	5.2±2.3;6 (0-10)	0.43
Tension	3.8±1.9;4 (0-10)	4.8±1.8;6 (2-8)	4.7±2.4;4 (0-10)	0.17
WBS 0-30 min Difference Score	4.2±2.1;4 (0-8)	4.5±2.5;4 (0-10)	4.8±2.3;4 (0-10)	0.37
Gender				
Female	4.2±2.2;4 (0-8)	4.5±2.5;4 (0-10)	4.8±2.6;4 (0-10)	0.79
Male	4.1±2.1;4 (0-8)	4.3±2.7;4 (0-8)	4.8±2;4 (0-8)	0.39
Age	43±13;42 (17-71)	38±13;38 (17-73)	41±17;37 (17-91)	0.11

It was determined that there was no difference in the frequency of analgesic use in the histories of the patients in terms of the efficacy of the treatments (p>0.05) (Table 3).

Table 3 The Effect of Analgesic Use on Treatment

	$\bar{x}$ ± SD; Median (min-max)	**P-value**
Metoclopramide+100 cc SF		
No History of Analgesic Use	4.3±2.3; 4 (0-8)	0.52
Analgesic Use History Once a Month	4.2±2; 4 (0-8)	
Analgesic Use History Once a Week	3.6±2; 4 (0-6)	
Analgesic Use History Two or More Per Week	5.5±1.9; 5 (4-8)	
Oxygen+100 cc SF		
No History of Analgesic Use	4.5±2.7; 4 (0-10)	0.71
Analgesic Use History Once a Month	4.9±2.5;6 (0-8)	
Analgesic Use History Once a Week	4.3±1.9;4 (2-8)	
Analgesic Use History Two or More Per Week	4±2.9;4 (0-10)	
Paracetamol		
No History of Analgesic Use	4.8±2.1;4 (2-10)	0.29
Analgesic Use History Once a Month	4.3±2.3;4 (0-10)	
Analgesic Use History Once a Week	5.4±2.4;6 (0-10)	
Analgesic Use History Two or More Per Week	5.6±2.6;6 (2-8)	

According to the randomization table, 15.3% (n=33) of the patients were administered salvage therapy with methimazole sodium. The percent of the non-responsive to the treatments were 9.8% (n=21) in migraine patients and 5.1% (n=11) in tension-type headache patients. In our study, there was no statistically significant difference (p=0.127) in terms of administering methimazole sodium as a salvage treatment in all groups (Table 4).

Table 4 Efficacy of Salvage Therapy in Primary Headache Methimazole Sodium Treatment

	Metoclopramide		**Oxygen**		**Paracetamol**		p
	n	%	n	%	n	%	
Administered	15	45.5	10	30.3	8	24.2	0.127
Not Administered	53	29.1	57	31.3	72	39.6	

Four patients who did not respond to the methimazole sodium which is the salvage therapy were evaluated as resistant headache patients and hospitalized in the neurology clinic. In the neurology clinic, when their follow-up and treatments conducted, one of these patients was diagnosed with Neuro-Behcet's disease and the other was diagnosed with a saccular aneurysm. In the etiology of the other two patients, no reason that causes secondary headache was found.

4. Discussion

Oxygen therapy, which is the most effective treatment for cluster headaches, was applied to the all primary headache patients, for the comparison of the efficacies of metoclopramide and paracetamol protocols. In our study, there was no statistical significance of efficacies between treatment protocols. Oxygen treatment effectiveness was found to be similar to the metoclopramide and paracetamol groups in migraine patients and tension type headache patients, and as well as in all type of primary headache patients without considering type classifications. Despite fewer of cluster type headache patients in our study, the efficacy of oxygen therapy was not statistically insignificant and not inferior to the other treatment groups, therefore it was as effective as the other treatments in primary headaches (p=0.37). As a conclusion, in our opinion, first-line treatment of the primary headaches should be oxygen therapy and hydration instead of the other conventional drugs, such as opioid drugs, non-opioid analgesics, and non-analgesic drugs, in terms of their higher costs, drug addiction and

their possible side effects.

In general practice, various analgesics and non-analgesic methods are used in the acute treatment of primary headaches worldwide. NSAIDs are often used in the acute treatment of headache in emergency departments [8, 9]. The analgesic agents used in the treatment have various degrees of side effects such as gastritis, gastrointestinal bleeding, nephropathy, and drug interactions. Also, analgesic use can cause headache both to become chronic and resistant to treatment [10, 11].

In the United States, opioids and barbiturates are frequently used in the treatment of migraine patients [12]. However; addiction should develop in patients depending on the frequent use of the opioids and barbiturates. For this reason, studies are still carried out to reduce opioid use in the treatment of migraine attacks but have not reached in desired rates [12, 13]. Friedman BW et al. suggested that the use of non-opioid drugs in migraine treatments should be chosen as the primary treatment approach [12]. In America and Europe, the most common reason for liver failure is the usage of paracetamol [14, 15]. For this reason, it shouldn't be the first option to be used in primary headaches. Ruzek M et al. reported that opioid use and prescription were gradually decreasing in the treatment of headaches. However, it was also emphasized that the use of non-opioid analgesics, dexamethasone, antihistaminic and dopaminergic receptor antagonists in place of opioid analgesics increased [16]. In the literature, since opioids have excessive side effects and more severe relapses, NSAIDs have been suggested [8, 17].

Non-opioid analgesics, metoclopramide, and oxygen therapy are used in the treatment of primary headaches in emergency departments in Turkey [18, 19]. Metoclopramide, which is one of the non-analgesic methods, has serious side effects such as dystonia, dyskinesia, and akathisia [9, 20]. Akathisia, observed in the study of Friedman BW et al. due to metoclopramide usage wasn't determined in our research [21]. Even so, metoclopramide shouldn't be a primary option in case of extrapyramidal side effects.

Oxygen therapy as a first choice in cluster headaches has some advantage points such as no known side effect, low costs and repetition [22]. In pathophysiology, the primary headache has a mostly functional impairment, instead of structural impairment, which has little effects on its pathology. Therefore, it is meant to treat primary headaches with oxygen. Unresponsiveness to oxygen should be a warning signal for secondary headaches. When considering its safety, it's possible to use in repeated doses and low costs, oxygen therapy has unquestionable advantages in treatments in primary headache. In literature, it is recommended to give 100% oxygen to the headache patients at a flow rate of 12-15 L/min [2, 5, 6, 23]. In our study, we gave oxygen treatment without discriminating the etiology of the primary headache.

It was observed in the studies conducted that IV hydration was also effective in the acute treatment of primary headaches [24, 25]. In order to eliminate the patient bias in the oxygen group in our study, hydration with 100 mL isotonic saline solution IV along with the oxygen was provided. However, Naeem F et al. reported in their review study that studies of the efficacies of hydration in headache were not meaningful [22] and Orr SL et al. found inefficacious in their study [24]. On account of these, the placebo effect of hydration was ignored in our study, because of the small amounts of liquid given and, therefore, the efficacy of the hydration in the acute treatment of primary headache could not be determined and studied.

In conclusion, nasal oxygen +100 mL isotonic saline hydration protocol was found to be effective in the acute treatment of primary headaches. This was considered the efficacy of oxygen treatment. In the treatment of primary headache attacks, oxygen therapy was found to be a reasonable treatment, regulating the functional impairment of headaches

4.1. Limitations

Due to the different application routes of nasal oxygen and the intravenous treatments of the study, blindness cannot be done. To overcome this bias, small amount of saline infusion was concomitantly applied to the oxygen therapy group. Although, the effects of this saline hydration on the treatments were ignored when establishing treatment protocols, it was not possible to make a distinction between whether hydration or oxygen was effective. In our study, hydration was given in small amounts, and the treatment efficacy was thought to be caused by nasal oxygen, instead of hydration.

Though oxygen therapy is obviously lesser costs than other treatments, cost/effective analysis has not been performed in this study.

In order to generalize the results, it should be considered to study with larger populations. Results can't be generalized due to single-centered research. Multi-center studies are needed.

5. Conclusion

As a conclusion, we found that, there was no superiority between the paracetamol, metoclopramide, and oxygen therapy efficacies in the treatment of the primary headaches. In the acute treatment of the primary headaches, we do not suggest the usage of paracetamol, which can cause liver failure; and metoclopramide, which can lead to extrapyramidal side effects. Since the similar effectiveness in the treatment, we strongly suggest oxygen therapy as first-line therapy in primary headache, which has not statistically difference in efficacy, without known side effects and can be used repeatedly if require.

Conflict of Interest and Funding

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