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Randomized Double-Blind Comparison of Intravenous Ibuprofen and Dexketoprofen in the Acute Treatment of Tension-Type Headache

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Abstract: Non-steroidal anti-inflammatory drugs are used routinely and first choice in the acute treatment of tension-type headaches (TTH). The aim of this study is to compare the analgesic efficacy of parenterally administered single dose dexketoprofen and ibuprofen in the treatment of TTH. Our study was designed in a randomized, double-blind model. Patients with tension headache were randomized to dexketoprofen and ibuprofen groups. Pain scores of the patients were recorded at 0, 15, 30, and 60 minutes with a 10-unit Numeric Rating Scale (NRS). Of these patients, 45 (50%) were included in the group to receive dexketoprofen treatment, and 45 (50%) to receive ibuprofen treatment. In total, 54 of our patients were female and 36 were male. The differences in mean NRS scores in the group treated with analgesic 1 were 2.0, 4.0, 5.22, 6.0 at the end of the 5th, 15th, 30th and 60th minutes, respectively, and 2, 5, 6.36, 7 for analgesic 2, respectively. While there was no significant difference between drug efficacy at all time points except the 30th minute, the efficacy of ibuprofen in reducing pain was more significant at the 30th minute (p=.015). As a result of our study, there was no significant difference between the analgesic efficacy of parenterally administered dexketoprofen 50 mg and ibuprofen 800 mg at the end of the 60th minute, while ibuprofen 800 mg was superior in terms of analgesic efficacy at the 30th minute.

Keywords: tension type headache, dexketoprofen, ibuprofen, emergency department, numerical rating scale

Gerilim Tipi Baş Ağrısının Akut Tedavisinde İntravenöz İbuprofen ve Deksketoprofenin Randomize Çift Kör Karşılaştırılması

Özet: Gerilim tipi baş ağrılarının (GTBA) akut tedavisinde nonsteroid antiinflamatuar ilaçlar rutin ve ilk tercih olarak kullanılmaktadır. Bu çalışmanın amacı, GTBA tedavisinde parenteral olarak uygulanan tek doz deksketoprofen ve ibuprofen'in analjezik etkinliğini karşılaştırmaktır. Çalışmamız randomize, çift kör bir modelle tasarlandı. Gerilim tipi baş ağrısı olan hastalar deksketoprofen ve ibuprofen gruplarına randomize edildi. Hastaların ağrı skorları 10 üniteli Numerik Rating Skala (NRS) ile 0, 15, 30 ve 60. dakikalarda kaydedildi. Bu hastalardan 45'i (%50) deksketoprofen tedavisi alacak gruba, 45'i (%50) ibuprofen tedavisi alacak gruba dahil edildi. Hastalarımızın 54'ü kadın, 36'sı erkekti. Analjezik 1 ile tedavi edilen grupta ortalama NRS skorlarındaki farklar sırasıyla 5, 15, 30 ve 60. dakikaların sonunda 2.0, 4.0, 5.22, 6.0 ve analjezik 2 için sırasıyla 2, 5, 6.36, 7 idi. Otuzuncu dakika dışında tüm zaman noktalarında ilaç etkinliği arasında anlamlı bir fark bulunmazken, ibuprofenin ağrıyı azaltmadaki etkinliği 30. dakikada daha anlamlıydı (p=.015). Çalışmamız sonucunda 60. dakika sonunda parenteral

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uygulanan deksketoprofen 50 mg ile ibuprofen 800 mg'ın analjezik etkinliği arasında anlamlı fark bulunmazken, ibuprofen 800 mg'ın analjezik etkinliği 30. dakikada daha üstündü.

Anahtar kelimeler: gerilim tipi baş ağrısı, deksketoprofen, ibuprofen, acil servis, nümerik derecelendirme ölçeği

INTRODUCTION

Tension-type headache (TTH) is the most common type of primary headache in the general population. TTHs can usually be diagnosed by the absence of features of other types of headaches (especially migraines). This relatively atypical feature of TTH makes it the least noticeable of the primary headache phenotypes. In addition, although it has a very high socioeconomic impact, there are few TTH studies among primary headache disorder studies (Veys et al., 2016). Although TTHs are common between the ages of 20-50, they peak between the ages of 30 and 40 (Stone et al., 2010; Bigal et al., 2000).

TTH patients can be treated medically or nonmedically (Jensen & Olesen, 1996). Medical TTH treatments can also be divided into two groups: acute TTH and chronic TTH treatment. Simple nonsteroidal anti-inflammatory drugs (NSAIDs) can also be given to stop any attack seen in patients or to reduce pain levels (Coskun, 2008).

Ibuprofen (Ibu) is the most used and prescribed NSAID. It is a nonselective inhibitor of cyclooxygenase-1 and cyclooxygenase-2. Although its anti-inflammatory properties are weaker than some other NSAIDs, ibuprofen has significant analgesic and antipyretic activity. Its effectiveness depends on the inhibitory effects on cyclooxygenases involved in the synthesis of prostaglandins (Bushra & Aslam, 2010).

Dexketoprofen (Dex) trometamol is a water-soluble salt of the dextrorotatory enantiomer of the NSAID ketoprofen. Racemic ketoprofen is used as an analgesic and anti-inflammatory agent and is one of the most potent in vitro inhibitors of prostaglandin synthesis (Barbanoj et al., 2001).
Various studies have treated patients with TTH using both drugs. Although administration routes and dosages varied among these studies, they often concluded that these two drugs do not have any superiority to one another (van Gerven et al., 1996; Lange & Lentz, 1995).

The main purpose of our study was to compare the analgesic efficacy of parenterally administered Dex trometamol 50 mg and Ibu 800 mg in TTH patients.

MATERIALS and METHODS

We conducted the research in accordance with a prospective, randomized, controlled, and double-blinded research model. Approval for the study was obtained from the Ethics Committee of Erzurum Atatürk University Faculty of Medicine (September 19.2018/6-2).

We included patients 18 years of age and older who were admitted to Atatürk University Research Hospital's Emergency Medicine Clinic with complaints of headache that met the diagnostic criteria for TTH in the third edition of the *International Classification of Headache Disorders*. Volunteers were required to speak and read Turkish and have stable vital signs. Our initial study population consisted of patients who were diagnosed with TTH among the patients who were admitted to the emergency department with the complaint of headache. After excluding patients without TTH diagnoses, our final sample? consisted of 90 participants.

We excluded patients who were under the age of 18, pregnant, allergic to any drug used in the study, had any contraindications for the use of these drugs (such as acute kidney failure, recent bypass surgery, or liver failure), or who did not volunteer to participate in the study. Patients who had used any

analgesic medication within 6 h prior to admission, were mentally retarded or could not cooperate, were hearing impaired, or who had underlying organic neurological disorders were also excluded from the study.

The patients were given detailed information about the drugs used in the study, along with the list of drugs that could be administered, and all patients signed an informed consent form. Patients who chose to participate in the study were taken to a private room in the emergency department and the protocol was started. We recorded patients' pain scores on a numeric rating scale (NRS) from 0-10. Patients marked pain scores on the evaluation forms before and during the procedure regardless of the previous point. On the same form, we also recorded patients' anesthetic numbers (group numbers), file numbers, ages, genders, and admission dates and times. During the procedure, we monitored SpO_2 levels, blood pressure, heart speed and rhythm, and body temperature with a Nihon Kohden® BSM-2301K branded device. Pain degrees were recorded at 0, 15, 30, 45 and 60 min. Any additional symptoms were recorded on patients' data sheets.

At follow-ups, we recorded patients' initial and disease characteristics per the literature: we noted age, gender, presence of chronic disease, vital signs, complaint on admission, onset time, pain localization, pain distribution, previous analgesic use and time used, and treatment given. Case report forms consisted of self-reported pain scale ratings at 0, 5, 15, 30, and 60 min; whether a rescue medication was used; and whether patients experienced any side effects.

The principal investigator carried out randomization using a computer program. In this computer program (LibreOffice), Analgesics 1 and 2 were numbered and assigned to participants in groups of equal size. The study nurse administered the medications as listed. The nurse who administered the drug then left the patient's treatment and follow-up. Neither the researchers nor the patients knew which drug had been administered to everyone. The study was explained to a physician who did not know the drugs to be administered and was conducted by that physician.

Statistical Analysis

We analyzed data using SPSS software (Version 20). Data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. We evaluated continuous variables' distribution using the Shapiro–Wilk test. We used an independent samples t test when groups met normal distribution conditions, and a Mann–Whitney u test otherwise. $p < 0.05$ was used for statistical significance.

RESULTS

90 patients (67% female) were included in our study. The Dex and Ibu groups were not equal. Pain onset time was Dex 360 minutes and Ibu 360 minutes. But the baseline characteristics of the two groups were similar as seen in Table 1.

Table 1. Distribution of patients in the treated groups.

	Treatment applied				**T**	**P**
	Dexketoprofen		**Ibuprofen**			
	Mean±SD	**Med (Min-Max)**	**Mean±SD**	**Med (Min-Max)**		
Age (years)	39±13	38 (19-69)	42±14	41 (18-69)	-0.772	0.442
SBP (mmHg)	126±11	127 (105-147)	123±13	123 (97-150)	1.065	0.290
DBP (mmHg)	78±9	78 (60-102)	77±9	76 (61-108)	0.166	0.868

Pulse (/min)	83±11	83 (65-120)	83±12	82 (63-105)	-0.028	0.978
RR (/min)	17±2	16 (15-20)	17±2	17 (12-21)	-1.477	0.143
Fever (°C)	36.50±0.2	36.5 (36.0-37.0)	36.5±0.3	36.5 (36.0-37.0)	-0.280	0.780
SO2 (%)	96±2	96 (92-99)	96±2	96 (91-100)	0.052	0.959
Onset of pain	1291±328	360 (30-2160)	528±680	300 (60-2880)	1.525	0.134

In our study, according to the NRS scores for both drugs, the highest degree of pain was detected at the time of admission. NRS scores tended to decrease over the hour-long period. Patients' most frequent NRS score upon admission was 6 points, while the lowest initial pain score was 4 points. 14 patients scored 10 points on the NRS scale, expressing excruciating pain at admission. Considering the mean and decrease in NRS scores, we observed similar large decreases in pain scores at 1 h in both groups. Table 2 shows the differences between NRS scores upon arrival and at 5, 15, 30, and 60 min for Groups 1 and 2.

Table-2. Follow-up course of pain degrees in drug groups.

			NRS- Mean ± SD	NRS- Med (Min-Max)	Chi-square	P
Treatment applied	**Dexketoprofen**	Nrs-0	7.07 ± 1.76	7.0 (4.0-10.0)		
		Nrs-5	5.29 ± 2.29	5.0 (0.0-10.0)		
		Nrs-15	3.16 ± 2.50	3.0 (0.0-9.0)	163.3	<0.001
		Nrs-30	1.84 ± 2.13	1.0 (0.0-8.0)		
		Nrs-60	0.87 ± 1.56	0.0 (0.0-6.0)		
	Ibuprofen	Nrs-0	7.49 ± 1.49	7.0 (5.0-10.0)		
		Nrs-5	5.29 ± 1.89	5.0 (0.0-10.0)		
		Nrs-15	2.73 ± 2.34	3.0 (0.0-9.0)	165.9	<0.001
		Nrs-30	1.13 ± 1.49	1.0 (0.0-5.0)		
		Nrs-60	0.49 ± 0.92	0.0 (0.0-4.0)		

The decreases in NRS values for both drug groups were generally significant and similar (see Table 3). We observed that Ibu achieved faster and superior analgesic effectiveness to Dex at 30 min.

Table 3. Comparison of the efficacy of analgesic agents.

	Treatment applied					
	Dexketoprofen		**Ibuprofen**			
	Mean±SD	**Med (Min-Max)**	**Mean±SD**	**Med (Min-Max)**	**Z**	**P**
Difference 0-5	1.78 ± 1.36	2.0 (0.0-5.0)	2.20 ± 1.46	2.0 (0.0-7.0)	-1.178	0.239
Difference 0-15	3.91 ± 2.07	4.0 (0.0-9.0)	4.76 ± 2.32	5.0 (1.0-10.0)	-1.625	0.104
Difference 0-30	5.22 ± 1.99	6.0 (0.0-9.0)	6.36 ± 1.96	6.0 (1.0-10.0)	-2.430	0.015
Difference 0-60	6.20 ± 1.97	6.0 (0.0-10.0)	7.0 ± 1.78	7.0 (1.0-10.0)	-1.708	0.088

We observed no side effects caused by the medications given to our participants. Three patients required rescue medication (Tramadol hydrochloride 50 mg): two in Dex and one in Ibu. A period of 90 days was determined for the study. During this period, all cases (90 cases) that met the criteria were included in the study. In addition to this method, the number of cases in the groups was balanced with the block randomization method (in groups of 6 cases) with the program we mentioned previously in the text.

No sample size analysis was performed in this study. In the post hoc power analysis performed by using the mean and standard deviation values of the "Difference 0-30" parameter, which was found to be statistically significantly different between the two groups, the Type-1 error was 5%. With a sample size of $n = 45$ in each group considered, the study's predictive power was 79%.

DISCUSSION

Simple analgesics; NSAIDs; and agents such as caffeine, codeine, and anxiolytics may be administered in combination to relieve pain in patient groups presenting with TTH attacks (Kahriman & Zhu, 2018). We aimed to compare the efficacy of Dex and Ibu from the NSAID group in treating TTHs. To the best of our knowledge from the literature, this was the first study to compare intravenous 800 mg Ibu with 50 mg Dex in TTH treatment. In our study, the female/male ratio was calculated as 1.5:1 out of 90 patients who were admitted to the emergency department with TTH. Although our sample size was not as large as Russel and Lavados et al. studies reporting similar female/male ratios, it is compatible with these studies (Russell, 2005; Lavados & Tenhamm, 1998). Data on age dependence of TTHs are limited. In a population-based study in the US, the prevalence of episodic TTH was reported to have peaked in patients' 40s (CITE). Demographic data were reported as 75-85% female, and the mean age was 37 (min = 18, max = 73) (Diamond et al., 2000). In our study, we obtained a similar mean patient age (Dex: 39±13, Ibu: 42±14). Mild or moderate pain is a diagnostic criterion for TTHs (Headache Classification Committee of the International Headache Society, 2013). Our groups' median NRS score on admission was 7 points, and the lowest NRS values reported by patients started at 4 points. Ibu and Dex can cause mild side effects, but these are not encountered very often (Busson, 1986; Packman et al., 2000; Diamond, 1983; Packman et al., 2015).

We did not observe any side effects in our patient population. Possible reasons for this may be that our sample size was not large enough, that we only observed patients for 60 minutes, or that mild side effects (such as nausea) occurred after patients left the hospital. In addition, our patients did not return to the emergency department; indeed, both patient groups tolerated these treatments well.

In one study, 50 mg of ketoprofen was more effective than a 200-mg dose of Ibu (van Gerven et al., 1996). However, there are also some studies in which low doses of both drugs yielded similar efficacy (van Gerven et al., 1996; Lange & Lentz, 1995). While most nonnarcotic analgesics have equivalent effects on TTHs, Ibu's generally favorable side-effect profile makes it a reasonable first choice (Verhagen et al., 2006).

Although our findings supported the literature overall, some of our results did not concur with extant studies. The activities of Dex and Ibu generally worked at similar levels except at 30 min after administration, but we observed no significant difference between their effectiveness after 1 h.

As a result, there was no difference between the analgesic activities for Ibu and Dex at the end of the 1-hour period, and they provided significant relief and improvement in the patients' pain.

In this study, where we demonstrated the efficacy of both drugs, the data in Table 1 (distribution of effects) and median NRS scores were similar, indicating that we directly assessed the difference in analgesic efficacy of the two drugs.

CONCLUSION

We found that Ibu has little or no side-effect profile. We did not observe a significant difference between the analgesic efficacy of Ibu 800 mg form and Dex 50 mg form after 1 hour. Ibu can be preferred primarily due to its rapid analgesic effectiveness and minimal side effects against TTHs. Prospective

studies with more patients and follow-up studies with longer-term effects and side effects will contribute greatly to the literature and improve our results.

Limitations

One of the limitations of our study is that we did not calculate the required sample size beforehand; however, we believe that the 79% power level found in post hoc analysis is acceptable.

It should also be noted that we do not evaluate patients after 60 minutes. We used the NRS as the pain scale because of its ease of administration. His sensitivity has been acknowledged in some publications; however, some consider the Visual Pain Scale to be more sensitive.

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