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ORIGINAL ARTICLE

Comparison of analgesic efficacy of ibuprofen and dexketoprofen in pain management of long bone fractures: a prospective, randomized, double-blind study

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Abstract

Introduction Long bone fractures (LBF) often cause severe pain, impacting patients' quality of life. This prospective, randomized, double-blind study aimed to compare the analgesic efficacy of dexketoprofen (Dex) and ibuprofen (Ibu) in LBF patients in the emergency department.

Methods Conducted between August 10, 2023, and January 17, 2024, the study included 100 eligible patients randomized into Dex and Ibu groups. Visual analog scale (VAS) scores were measured at baseline and at 30, 60, and 120 min. DeltaVAS (ΔVAS) values and ΔVAS percentages (ΔVAS%) were calculated. Primary endpoints were ΔVAS scores (ΔVAS 30-60-120) and ΔVAS% for comparative analysis.

Results Statistical analysis showed no significant difference in ΔVAS30 ($p = 0.359$). However, ΔVAS60 exhibited a significant difference ($p = 0.027$), as did ΔVAS120 ($p = < 0.001$). ΔVAS%30 showed no significance ($p = 0.224$), but ΔVAS%60 and ΔVAS%120 were clinically and statistically significant ($p = 0.017$ and $p = < 0.001$, respectively).

Conclusion Ibuprofen 800 mg demonstrated superior analgesic efficacy at 60 and 120 min compared to Dex in long bone fractures. These findings suggest ibuprofen's potential as an effective pain management option in emergency departments.

Keywords Long bone fractures · Dexketoprofen · Ibuprofen · Analgesic efficacy · Emergency department

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Introduction

Acute pain represents a pervasive challenge within emergency departments, impacting nearly 80% of patients [1]. Particularly in the context of acute trauma, pain can exacerbate central sensitivity, underscoring the imperative to address it effectively with analgesia tailored to this unique consideration [2]. Managing pain associated with emergency scenarios not only enhances patient comfort but also upholds a fundamental human right [1, 2]. Moreover, persistent pain and associated emotional states can trigger heightened chemical release and stress responses post-injury [3].

Despite the wealth of experience among emergency physicians, instances of oligoanalgesia may arise due to suboptimal dosing and selection of analgesics [4]. A study revealed that 33% of acute trauma patients received analgesic treatment, often misaligned with the severity of their pain [5]. Shockingly, only a third of individuals presenting to the emergency department with extremity fractures received appropriate analgesic intervention [6]. Long bone

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fractures (LBF), encompassing tibial, femoral, and humerus fractures, constitute approximately 4% of emergency department visits in the USA, amounting to 2 million visits annually [3, 7]. These fractures frequently induce severe pain, and efficacious pain control significantly contributes to the enhancement of patients' quality of life [1, 2].

The landscape of pain management in the context of LBF is multifaceted, considering the diverse reasons for their occurrence, the varied patient populations affected, and the need for a comprehensive array of approaches in their treatment [8]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently employed in the emergency department for pain management, specifically in patients with bone fractures [9–11]. Despite their common usage, there exists no definitive evidence-based recommendation regarding the choice of NSAIDs for this indication. Dexketoprofen (Dex) and ibuprofen (Ibu) stand as illustrative examples within this drug category, with current literature suggesting similarities in their pharmacodynamic properties while hinting at potential distinctions in specific indications [9, 10].

The objective of this randomized, controlled, double-blind study was to assess the pain-controlling effectiveness of Dex 50 mg and Ibu 800 mg in the context of LBF, utilizing the visual analog scale (VAS) as the primary evaluation metric.

Material and method

Study design

This prospective study was conducted as a randomized controlled trial with a double-blind design. The research took place at Ankara Bilkent City Hospital, a tertiary emergency medicine training hospital. Patients aged 18–65, presenting with LBF at the hospital's emergency department between August 10, 2023, and January 17, 2024, were screened for potential inclusion in the study. Ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee No. 2 (Date: 09/08/2023—No.: E2-23-4743). The study protocol was also registered with ClinicalTrials.gov (NCT06060236).

Patient selection

Patients aged between 18 and 65, diagnosed with shaft fractures in the femur, tibia, and humerus bones resulting from trauma, commonly referred to as long bones, were eligible for inclusion in the study. These individuals, managed with long leg or long arm splints and scheduled for surgery following premedication by the orthopedist, were enrolled in the research. All patients received comprehensive information about the study procedures. Written informed consent, along with signatures, was obtained from volunteers who willingly agreed to participate in the study.

Exclusion criteria

The following criteria were applied to exclude certain individuals from participation in the study:

- Patients exhibiting unstable vital signs
- Patients with a history of adverse reactions to NSAIDs
- Those incapable of determining pain intensity on the VAS due to mental retardation or visual impairment
- Patients presenting with a VAS < 50 mm
- Patients with open fractures
- Cases requiring fracture reduction
- Patients designated for full circular plaster application
- Patients with additional injuries to vital organs
- Pregnant women and those suspected of being pregnant
- Patients with advanced systemic diseases
- Individuals diagnosed with malignancy
- Those with chronic liver and kidney diseases
- Individuals using neuro-psychiatric drugs with sedative and analgesic effects
- Patients with a history of psychiatric and neurological diseases
- Individuals who used analgesics within 12 h prior to admission

Intervention

Patients in the respective treatment groups received either 800 mg Ibu (Intrafen, GEN Pharmaceuticals, Turkey, 800 mg/8 mL) or 50 mg Dex (Arveles, Menarini Pharmaceuticals, Spain, 50 mg/2 mL). Both medications were administered via intravenous (IV) infusion over 15 min in 150 mL of normal saline. To maintain uniformity and mask volumes, 6 mL of normal saline was added to the Dex group during preparation. Concurrently, the patients' long arm or long leg splints were practically prepared and applied during this 15-min period.

The principal investigator, responsible for study planning, conducted randomization using a contemporary online tool for generating random numbers. Subsequently, a separate individual, following the randomization order,

prepared drug mixtures and placed them in treatment boxes. The drugs designated for the treatment groups shared similar appearances and properties, ensuring that evaluating personnel, including the doctor and nurse unaware of the patients' groups, remained uninformed during both the assessment and implementation stages.

In case the VAS score remained at 50 mm or above after 120 min, rescue treatment was planned. Intravenous tramadol hydrochloride (Contramal, Abdi İbrahim Pharmaceuticals, Turkey, 100 mg/2 mL) was intended to be administered at a dose of 100 mg in 30 min, diluted in 500 mL normal saline.

Outcomes

The assessment of patients' pain levels commenced upon admission, utilizing the VAS. Patients were instructed to mark their pain on a visual scale ranging from 0 (indicating no pain) to 100 mm (representing the worst pain ever experienced) [12]. The VAS score at the emergency department admission was documented as VAS0 in the case report form. The goal was to initiate analgesic treatment for each patient within a maximum of 15 min. Subsequently, the VAS scores at the 30th, 60th, and 120th minutes post-treatment initiation were recorded as VAS30, VAS60, and VAS120, respectively. Changes in the VAS score (delta-VAS) at these time points concerning VAS0 were calculated as ΔVAS30, ΔVAS60, and ΔVAS120 using statistical software. Additionally, the average values of ΔVAS as a percentage (ΔVAS%) relative to VAS0 were computed. For instance, the mean percentage reduction between VAS0 and VAS30 was determined using the formula $(\Delta VAS30 / VAS0) \times 100$.

The primary endpoint of the study focused on the statistical differences in "ΔVAS 30/60/120" and "ΔVAS% 30/60/120" values between the two treatment groups during the treatment period. Secondary outcome measures included differences between the groups in the requirement for rescue treatment, observed side effects, and other recorded variables.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for MacOS, Version 28.0 (Armonk, NY: IBM Corp). To assess normality in continuous data, the Shapiro–Wilk test, Q-Q plots, and histogram were employed. Normally distributed parameters were presented as mean, standard deviation, and 95% confidence interval, while non-normally distributed parameters were expressed as median and interquartile range. The Mann–Whitney *U* test compared medians between the two groups for non-normally distributed parameters, and the independent samples *t*-test assessed mean differences for normally distributed parameters. The comparative results of VAS0, VAS30, VAS60, and VAS120 scores between the groups are given in the error bar graph.

The Pearson chi-square test was utilized for comparing ratios of categorical data between the main groups. Boxplot plots were employed to visually illustrate differences in means for ΔVAS and %ΔVAS measurements. A significance level of $p < 0.05$ was considered for statistical significance.

Sample size

The sample size analysis, referencing the study by Friday JH et al., determined that a 16 mm reduction in pain on the VAS would be clinically significant. To achieve 80% power and maintain a 5% type-1 error rate, it was calculated that a minimum of 30 patients should be included in each group [13]. Accounting for potential data loss, the study was planned with a total of 100 patients, allocating 50 patients to each treatment group.

Results

Demographic and descriptive characteristics

The demographic and descriptive characteristics of the patients are summarized in Table 1. The study included 100 patients, with 50 in the Dex group and 50 in the Ibu group, and no patients withdrew from the study after randomization. The consort flow diagram illustrating the study design is presented in Fig. 1.

Among the participants, 24 (48%) were female in the Dex group and 19 (38%) in the Ibu group. The mean ± SD and median (25–75%) age of the participants were 51.7 ± 16–61 (41.25–65) in the Dex group and 49.6 ± 16.6–59 (33.75–63.25) in the Ibu group, respectively, with no statistically significant difference ($p = 0.35$). Height and weight distributions did not show statistical differences between the groups ($p = 0.77$; $p = 0.95$, respectively).

While participants did not specifically report or name any analgesics, a comparison of monthly analgesic usage frequencies revealed a statistically significant difference.

Table 1 Demographic, symptom, and background characteristics in Dex and Ibu groups

Variables		Treatment group						
		Dex			Ibu			*p*-value
		n (%)	Mean ± SD	Median (25–75%)	*n* (%)	Mean ± SD	Median (25–75%)	
Gender	Male	26 (52)			31 (62)			0.313*
	Female	24 (48)			19 (38)			
Age			51.7 ± 16	61 (41.25–65)		49.6 ± 16.6	59 (33.75–63.25)	0.351†
Height			167.6 ± 8.2	169.5 (161.5–174.25)		168.2 ± 9.1	170 (160–175)	0.769†
Weight			71.7 ± 13.2	73.5 (60.75–80		72.7 ± 14.5	74.5 (64.75–80)	0.948†
Analgesic usage frequency per month			1.2 ± 1.6	0.5 (0–2)		2.5 ± 3	2 (0–4)	0.010†
TA systolic			129.6 ± 15.6	140 (130–150)		130.6 ± 14.8	140 (130–150)	0.547 †
TA diastolic			77.2 ± 9.3	80 (70–81.25)		74.9 ± 17	80 (70–82)	0.918†
Pulse/minute			82.8 ± 9.8	83 (75.75–89.25)		79.7 ± 12.7	80 (75–87.25)	0.320†
Saturation %			96 ± 2.9	96 (94.75–98)		96.3 ± 1.9	96 (95–98)	0.970†
Respiratory rate/minute			17.6 ± 1.4	17 (17–18)		18.5 ± 2	18 (17–20)	**0.330**†
Side effect		1 (2)			1 (2)			**1.000**‡
Need for rescue medication		16 (32)			7 (16)			**0.032***
Fractured bone	Femur	31 (62)			26 (52)			0.299*
	Tibia	11 (22)			18 (36)			
	Humerus	8 (16)			6 (12)			

*Pearson chi-square test

†Mann–Whitney *U* test; median, interquartile range

‡Fisher's exact test

The median analgesic usage for patients in the Dex group was 0.5 (0–2), while for those in the Ibu group, it was 2 (0–4) ($p = 0.010$). No significant differences were observed in admission vital signs between the two groups. The distribution of fractured bones showed no statistical difference between the Dex and Ibu groups ($p = 0.299$).

Visual analog scale (VAS) analysis

The comparison of VAS scores among the groups at the 0th 30th, 60th, and 120th minutes is presented in Table 2 and Fig. 2. Statistically, a significant difference was observed only at VAS 120 ($p < 0.001$).

Table 2 and Fig. 3 present the VAS values of participants at different measurement points and the corresponding reductions at the 30th, 60th, and 120th minutes compared to baseline (ΔVAS30, ΔVAS60, ΔVAS120), analyzed by treatment groups. The percentage values of participants' ΔVAS compared to VAS0 (ΔVAS%) and the statistical outcomes of the inter-group comparisons are displayed in Table 2 and Fig. 3.

There was no statistical distinction between the two groups in ΔVAS30 [$p = 0.359$, mean diff (95% CI) = −2.82 (−8.89 to 3.25)]. However, a statistically significant difference emerged in ΔVAS60 [$p = 0.027$, mean diff (95% CI) = −7.20 (−13.56 to −0.83)], and the difference in ΔVAS120 values was also statistically significant [$p = < 0.001$, mean diff (95% CI) = −12.46 (−19.6 to −5.3)]. The mean ΔVAS% between groups showed no significant difference in ΔVAS%30 ($p = 0.224$, mean diff (95%CI) = −13.22 to 3.14). However, the means of ΔVAS%60 and ΔVAS%120 were clinically and statistically significant [for ΔVAS%60 and ΔVAS%120, respectively: $p = 0.017$, mean diff (95%CI) = −18.64 to 1.90; $p = < 0.001$, mean diff (95%CI): −25.66 to −7.48] (Table 2).

Regarding the need for rescue medication, 16 (32%) patients in the Dex group and 7 (14%) patients in the Ibu group required it, demonstrating a statistically and clinically significant difference ($p = 0.032$) (Table 1).

Fig. 1 Consort flow diagram

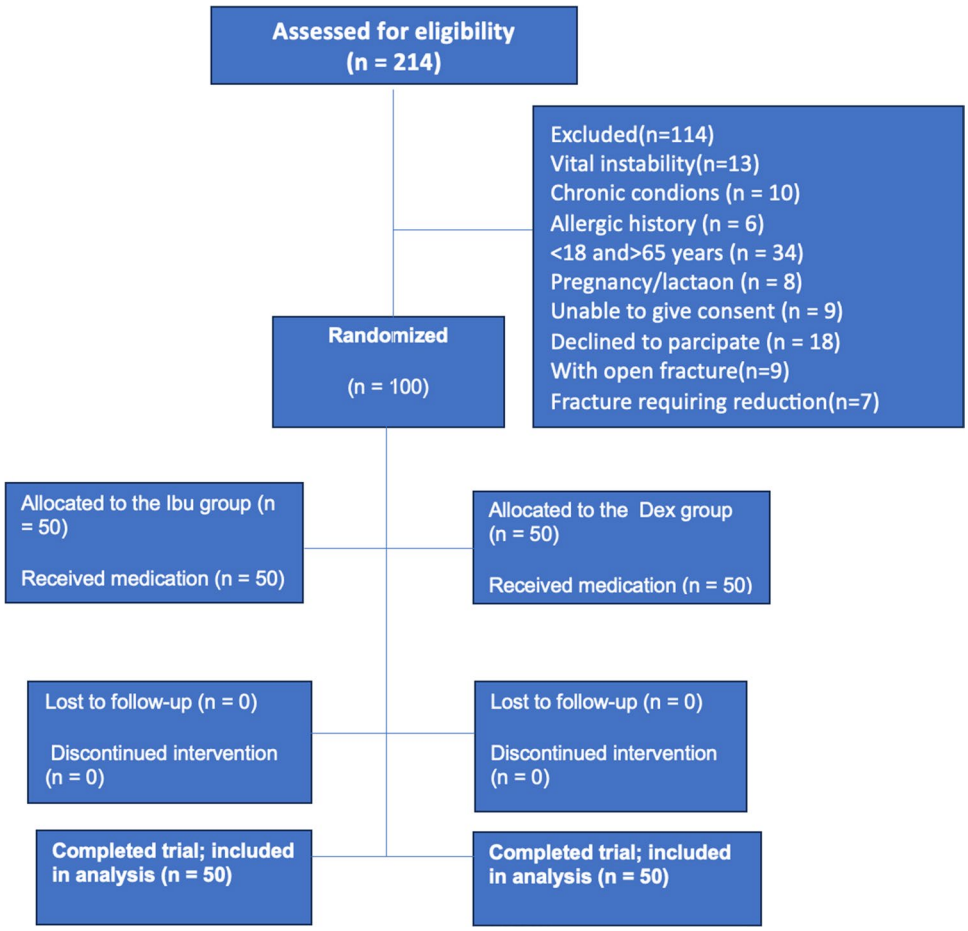

Table 2 Visual analog scale and differences between time periods

Variables	Treatment group					
	Dex		Ibu		*p*-value	Mean diff (95% CI)
	Median (25–75%)	Mean ± SD	Median (25–75%)	Mean ± SD		
VAS0	80 (62–97.25)		74.5 (63–86)		0.614*	
VAS30	48 (37.75–71.5)		47 (31–69.25)		0.245*	
VAS60	41.5 (26–58.25)		30 (22–51.25)		0.025*	
VAS120	36.5 (21.75–53)		21 (9.75–38.25)		< 0.001*	
ΔVAS30		23.9 ± 14.3		26.7 ± 16.2	0.359†	− 2.82 (− 8.89 to 3.25)†
ΔVAS60		32.9 ± 14.8		40.1 ± 17.2	0.027†	− 7.20 (− 13.56 to − 0.83)†
ΔVAS120		38.6 ± 14.6		51.0 ± 20.9	< 0.001†	− 12.46 (− 19.6 to − 5.3)†
ΔVAS%30		31.9 ± 18.3		36.9 ± 22.6	0.224†	− 13.22 to 3.14†
ΔVAS%60		43.9 ± 19.3		54.2 ± 22.7	0.017†	− 18.64 to − 1.90†
ΔVAS%120		51.5 ± 20		68.1 ± 25.5	< 0.001†	− 25.66 to − 7.48†

*Mann–Whitney *U* test; median, interquartile range

†Independent sample *t* test; mean ± SD

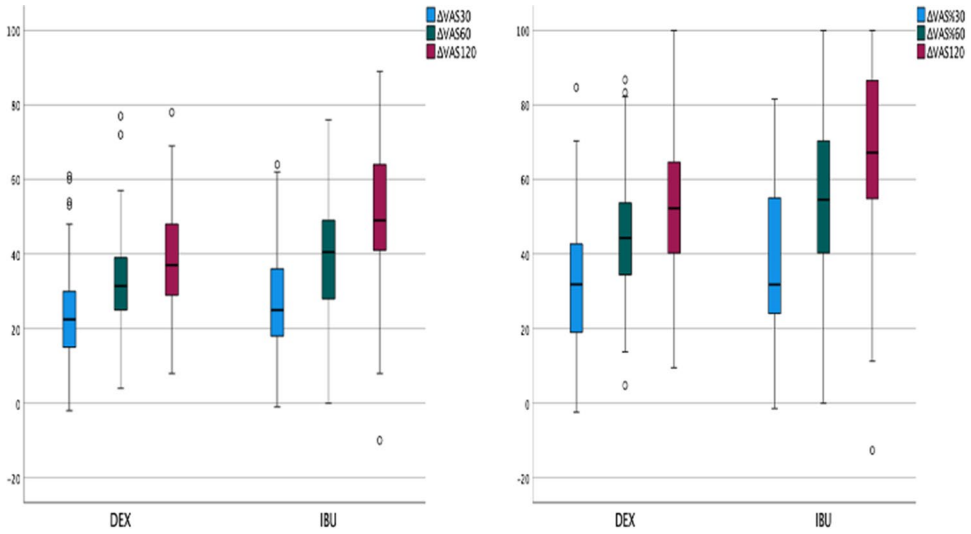

Fig. 2 Comparison of VAS scores among the groups at the 0th 30th, 60th, and 120th minutes

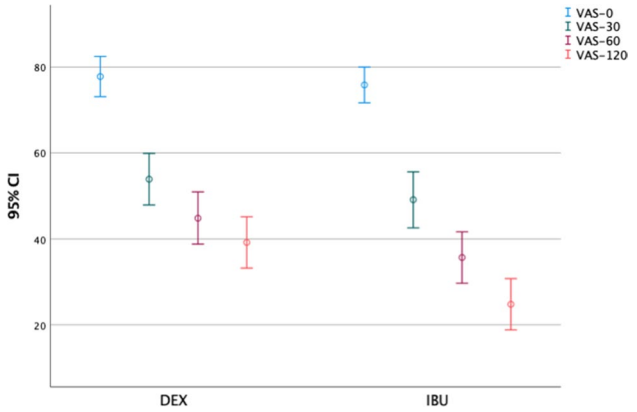

Fig. 3 VAS values of participants at different measurement points and the corresponding reductions at the 30th, 60th, and 120th minutes compared to baseline

Side effects

No side effects were reported except for mild nausea, which occurred in one patient from each group ($p = 1.00$). Importantly, no life-threatening side effects were observed in any patient throughout the study or during the follow-up period.

Discussion

The primary objective of our study was to assess and compare the analgesic efficacy of two distinct NSAID groups, Dex and Ibu, in patients presenting to emergency departments with LBF. The findings of this study indicate that Ibu demonstrates significantly higher efficacy and superior analgesic effects compared to Dex, particularly at the 60th and 120th minutes, as evidenced by ΔVAS and ΔVAS%. Notably, the Ibu group also exhibited a greater reduction in the need for rescue medication, highlighting a notable strength of our study.

It is crucial to underscore that our study stands as the first of its kind to juxtapose the analgesic effectiveness of intravenous Ibu 800 mg and Dex 50 mg specifically in the context of LBF.

Bone fractures are a condition that affects millions of people globally. One of the primary treatments for patients with extremity fractures in emergency departments is to effectively relieve or reduce pain. Effective management of pain is closely related to patient comfort [14]. It is known that pain control is often handled inadequately in emergency departments [15].

In the literature review, some studies on pain control of long bones have been encountered in recent years, but the majority of these are studies on opioids and their use methods. Maleki Verki and colleagues compared nebulized fentanyl and low-dose ketamine in LBF and reported that low-dose ketamine infusion was more effective [14]. In some different studies, it has been reported that when the analgesic activities of ketamine and morphine are compared, the difference is not statistically significant [16, 17]. When the studies were examined, while there were studies using drugs such as ketamine, morphine, and fentanyl in LBF, as a result of our screening, we did not find any study comparing Ibu and Dex in the pain control of LBF. In a general review published on acute and chronic pain, the high effectiveness of NSAIDs is mentioned [18]. When studies in which Ibu and Dex were used in other specific areas were examined, different results of the two analgesic agents were reported. Similar effectiveness of Ibu and Dex is mentioned in diagnoses such as low back pain, tension type, headache, migraine, and renal colic [19–22]. These

studies in the literature show similar and different results in terms of the analgesic effectiveness of the two drugs. However, it may not be appropriate to generalize these results to bone fractures.

In a study conducted on pediatric patients, comparing Ibu versus acetaminophen with codeine in the pain control of arm fractures, it was reported that the treatment failure rate of the Ibu group was 20% [23]. Additionally, in a study in which different doses of Ibu, paracetamol, and codeine were used for postoperative pain control, it was reported that 1 patient (2%) needed rescue medication after Ibu 800 [24]. In a study conducted by Yılmaz A et al. with 200 patients with musculoskeletal system trauma, they used paracetamol and Dex and reported that they included 100 patients in each group. They stated that 11 out of 100 patients in the Dex group needed rescue medication [25]. In a study conducted by Doğan C et al. using Ibu 400, paracetamol 1000 mg, and Dex 50 mg, they reported that there was no need for rescue medication in all three groups [19]. In addition, in another study conducted by Özdemir M and colleagues on renal colic patients, although there were four treatment groups, they also created an Ibu 800 mg and Dex 50 mg group and stated that there was no statistical difference in terms of the need for rescue medication [22]. In a study that included patients who applied to the emergency department with complaints of pain due to acute musculoskeletal system injury, it was reported that 36.6% of the patients in the Ibu group needed rescue medication. While our rates of need for rescue treatment in our study show similar rates to some trauma studies in the literature, some do not. The results in our study were clinically and statistically significant in favor of Ibu. In this case, it makes Ibu more preferable because opioids can have many side effects.

Although studies using two analgesic agents in LBF are limited, the lack of serious systemic side effects when the side effects are examined in studies using Ibu and Dex in other diagnostic groups is compatible with and supports the literature on this issue [26, 27].

The fact that the participants' age, gender, height, weight, vital values, broken bone type, and VAS0 scores did not show any statistical difference between the groups is an indication that the distribution of the groups in the study is similar. We consider this to be one of the strengths of our study. Pain intensity is generally very high in LBF, and a special evaluation for this specific group is one of the strengths of our study.

Limitations

It seems that studies are generally conducted with opioids and similar group drugs. In our study, this group of drugs was included as rescue analgesics. Although the results were satisfactory for the performance of both drugs in the study, different results may be obtained from a study comparing NSAIDs with opioids and similar groups. Another issue is that a placebo group was not created in the study. However, from an ethical perspective, it is clear that this group of patients cannot be deprived of analgesic treatment. Therefore, not having a placebo control in the study was considered a logical approach. In addition, since the superiority of both analgesic agents over placebo has been stated many times in the literature, this situation was not considered a limitation. Although we determined the number of our patients according to the power analysis, conducting it with a much larger patient population would have further increased the power of the study.

Conclusion

The absence of statistical differences in demographic data, vital signs, and VAS0 values at the patients' initial presentation indicates that the evaluation of analgesic efficacy in the study was conducted in a more unbiased and reliable manner. The superior outcomes of ΔVAS60 and ΔVAS120 values, as well as ΔVAS%60 and delta ΔVAS%120, in the Ibu group in the study suggest that Ibu is a more preferable analgesic. We recommend the use of 800 mg Ibu in LBF.

Author contribution S.D., A.S., N.I.I.: writing—review and editing, writing—original draft, visualization, validation, supervision, software, resources, project administration, methodology, investigation, formal analysis, data curation, conceptualization. B.K., K.Y.: conceptualization, formal analysis, methodology, validation, visualization, writing—original draft, writing—review and editing. I.A: writing—review and editing, writing—original draft, resources, project administration, investigation, formal analysis, data curation.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The author declares no competing interests.

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