Original Contribution

Intravenous paracetamol versus dexketoprofen in acute musculoskeletal trauma in the emergency department: A randomised clinical trial

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ABSTRACT

Introduction: Musculoskeletal system traumas are among the most common presentations in the emergency departments. In the treatment of traumatic musculoskeletal pain, paracetamol and non-steroidal anti-inflammatory analgesics (NSAID) are frequently used. Our aim in this study is to compare the efficacy of intravenous dexketoprofen and paracetamol in the treatment of traumatic musculoskeletal pain.
Methods: This prospective, randomised, double blind, controlled study was conducted in a tertiary care emergency unit. The participating patients were randomised into two groups to receive either 50 mg of dexketoprofen or 1000 mg of paracetamol intravenously by rapid infusion in 150 mL of normal saline. Visual analogue scale (VAS), Numeric Rating Scala (NRS) and Verbal Rating Scale (VRS) was employed for pain measurement at baseline, after 15, after 30 and after 60 mins.
Results: 200 patients were included in the final analysis. The median age of the paracetamol group was 34 (24–48), while that of the dexketoprofen group was 35 (23–50), and 63% (n = 126) of them consisted of men. Paracetamol and dexketoprofen administration reduced VAS pain scores over time (p = 0.0001). Median reduction in VAS score at 60 min was 55 (IQR 30–65) for the paracetamol group and 50 (IQR 30.25–60) for the dexketoprofen group. There was no statistically significant difference between the paracetamol and dexketoprofen groups in terms of VAS reductions (p = 0.613).
Conclusion: Intravenous paracetamol and dexketoprofen seem to produce equivalent pain relief for acute musculoskeletal trauma in the emergency department.
CLINICALTRIALS.GOV NO: NCT03428503

1. Introduction

Musculoskeletal system traumas are among the most common presentations in the emergency departments. In the US alone, there are about 66 millions physician visits per year due to musculoskeletal injuries. Musculoskeletal injuries account for 77% of all injury related presentations [1]. Most of these musculoskeletal injuries are composed of extremity trauma [1,2]. Besides, approximately 17 million emergency department visits include strains, sprains, and extremity contusions [2]. The aim of emergency analgesic treatment is to relieve the pain quickly, with the least undesirable side effects and without recurrence

after discharge, and pain management is a vital component of treatment [3,4]. In this sense, the choice of ideal treatment should be with a drug that has the least contraindications and the strongest analgesic activity. In the treatment of traumatic musculoskeletal pain, paracetamol and non-steroidal anti-inflammatory analgesics (NSAIDs) are frequently used although they have detrimental side effects [3,5]. Dexketoprofen is also a medicine from the NSAIDs group. Opioids provide effective and rapid analgesia, but they bring about side effects, such as hypotension, dizziness, nausea and vomiting [6]. In recent years, along with the production of parenteral forms of NSAIDs, the analgesic efficacy of these drugs has turned out to be an interesting topic for researchers [7,8]. In particular, the intravenous (IV) form of paracetamol is still newer than other NSAIDs, and the safety margin is wide and the incidence of side effects is low. The paracetamol IV form effectiveness and whether it proves to be an alternative to other analgesics or not remains one of

the important research topics of the day [9-11]. Both drugs are frequently used in the treatment of traumatic musculoskeletal pain in emergency services [5,12]. The onset of action (analgesia) of these drugs is faster in IV forms than oral form, which provides rapid discharge and reduces the monitoring time in a crowded emergency service [13].

The current study seeks to obtain data which will help to address the aforementioned issues by comparing the efficacy of IV dexketoprofen and paracetamol in the treatment of traumatic musculoskeletal pain. The hypothesis is that paracetamol is not inferior to the treatment with dexketoprofen. The use of paracetamol could reduce the use of NSAIDs and their adverse effects.

2. Methods

2.1. Study type

The study was approved by Pamukkale University Ethical Committee for Clinical Investigations with the decision number 57051259-020/7653 dated 29 January 2015 and numbered 2015/02. The study was registered and approved by the American clinical trial registry (NCT03428503 at https://clinicaltrials.gov).

Our research is an equivalence study.

2.2. Study population

Emergency patients with complaints of traumatic musculoskeletal system pain who agreed to participate in the study were included in the study group. Patients constituting the study group were admitted into the present study after being evaluated for inclusion and exclusion criteria. The current study was conducted at ED, Pamukkale University, Denizli, Turkey.

2.3. Subject selection

The patients with isolated musculoskeletal system trauma who had a trauma story in the last 48 h with a VAS pain score of 50 mm and above, with moderate–severe pain, 18 years old and older but younger than 65 years old, willing to participate the study were recruited in the study (females with reproductive potential and using a contraceptive method were also recruited). The patients were excluded if they did not give their consent, were not informed about the study since ED was too crowded, received analgesic before presenting ED, had comorbid diseases or symptoms such as DM, HT, CAD, Renal or Liver transplantation, had defined pregnancy or possibility, declared to have allergy to analgesics, were under 18 or >65 age, had major multiple trauma, and were admitted to ED repeatedly with the same trauma or after suicide.

2.4. Research protocol

When all trauma patients applied to emergency services, the first examinations were performed immediately. During the examination, VAS pain scores were taken and recorded by the examining physician as part of the standard procedure. A simple randomisation method was used for the study. An assistant, blind to the study, prepared the randomisation schedule by using a computer. A potentially eligible patient for the study was assigned a study number which was concealed in a sealed envelope after the informed consent was received by a physician outside the study. Until the end of the work, only this person knew the study numbers and the matching drugs.

The study groups and drug doses to be given were as follows:

Group 1: Paracetamol (1000 mg) (Perfalgan, Bristol-Myers Squibb, USA; 1 g in 150 mL normal saline).

Group 2: Dexketoprofen (50 mg) (Arveles, IE Ulagay-Menarini, Turkey, 50 mg in 150 mL normal saline).

One of the nurses charged in the emergency service was responsible for the preparation of the study drug and the other one, that is, the nurse ignorant of which drug was prepared, was responsible for the administration of the study drug. The previously allocated numbers were stored in non-transparent envelopes. The non-transparent envelope in the next order was opened by the study nurse and the study drug was prepared. The patients eligible for the study was admitted to the room called monitorized surveillance unit in the ED, and monitored and IV lines were inserted. The study drugs were calibrated by the nurse in charge of the emergency service and were administered by the other nurse. The drugs calibrated for each group were transparent and identical in appearance.

After randomisation, the drug to be administered was diluted in 150 mL of saline and administered as an IV fast infusion. At 0, 15, 30, and 60th minutes, the pain was assessed with NRS, VAS and VRS and was recorded by the examining physician. In the process, the patients were followed up through vital signs for potential side effects. The study was terminated at the 60th minute, in which the patients with ongoing pain (VAS pain score of 50 mm and above) was treated with 1 μg/kg of fentanyl as a salvage treatment. Fentanyl (Talinat) was taken from the hospital pharmacy by issuing a red prescription on behalf of the patient, and the fee was covered by the research budget. No other pain medication was used other than these drugs. The medicines administered in the study were prepared in accordance with the 'Good Manufacturing Practices' guidelines.

2.5. Data analysis

The data were recorded with Statistical Package for Social Sciences 17.0 (IBM Corp., SPSS Inc., Chicago IL, USA). Given that the difference between the related groups would have a small effect size (dz = 0.3), a power analysis was performed prior to the study. Accordingly, when 97 participants were included in the study, that would result in 90% power with 95% confidence level. We included 100 participants for Dexketoprofen group and 100 participants for Paracetamol group in the present study. For VAS results, we reached 100% power with 95% confidence for both drugs (par dz. = 2,51, dex dz. = 2,64). Descriptive criteria are presented as mean and standard deviation. The averages were given as mean ± standard deviation. Independent groups were analyzed by using chi-square, Mann–Whitney U test for non-normal distribution and Independent Samples t-Test for normal distribution. We used Kolmogorov–Smirnov test for normality. In statistically repetitive measurements (musculoskeletal pain VAS, NRS scores), the groups were compared using the Friedman Test. Further, VRS score change was compared with Pearson Chi-Square test. As in many other studies, statistical significance level was accepted as p < 0,05 in all analyzes.

3. Results

The patient recruitment for the study was between 10 January 2016–29 June 2017, when 4762 patients were admitted due to an acute trauma-induced musculoskeletal pain. Of these, 738 patients did not agree to be involved in the study, while 1542 patients were not informed about the study owing to the intense workload of the emergency department during the peak hours. 2282 patients with any of the exclusion criteria were not included in the study. The remaining 200 patients who had the inclusion criteria were recruited in the study. The flow chart of our study is as shown in Fig. 1 (Fig. 1).

126 patients were male (63%) and 74 (37%) were female. 100 patients received paracetamol, while the other 100 dexketoprofen. The median age of the paracetamol group was calculated as 34 (24–48), whereas that of the dexketoprofen group was 35 (23–50). At the beginning of the study, the mean value of systolic blood pressure was 120.37 ± 10.39 for the paracetamol group and 120.63 ± 8.57 for the dexketoprofen group. The mean value of diastolic blood pressure was 78.98 ± 5.2 for the paracetamol group and 78.55 ± 5.42 for
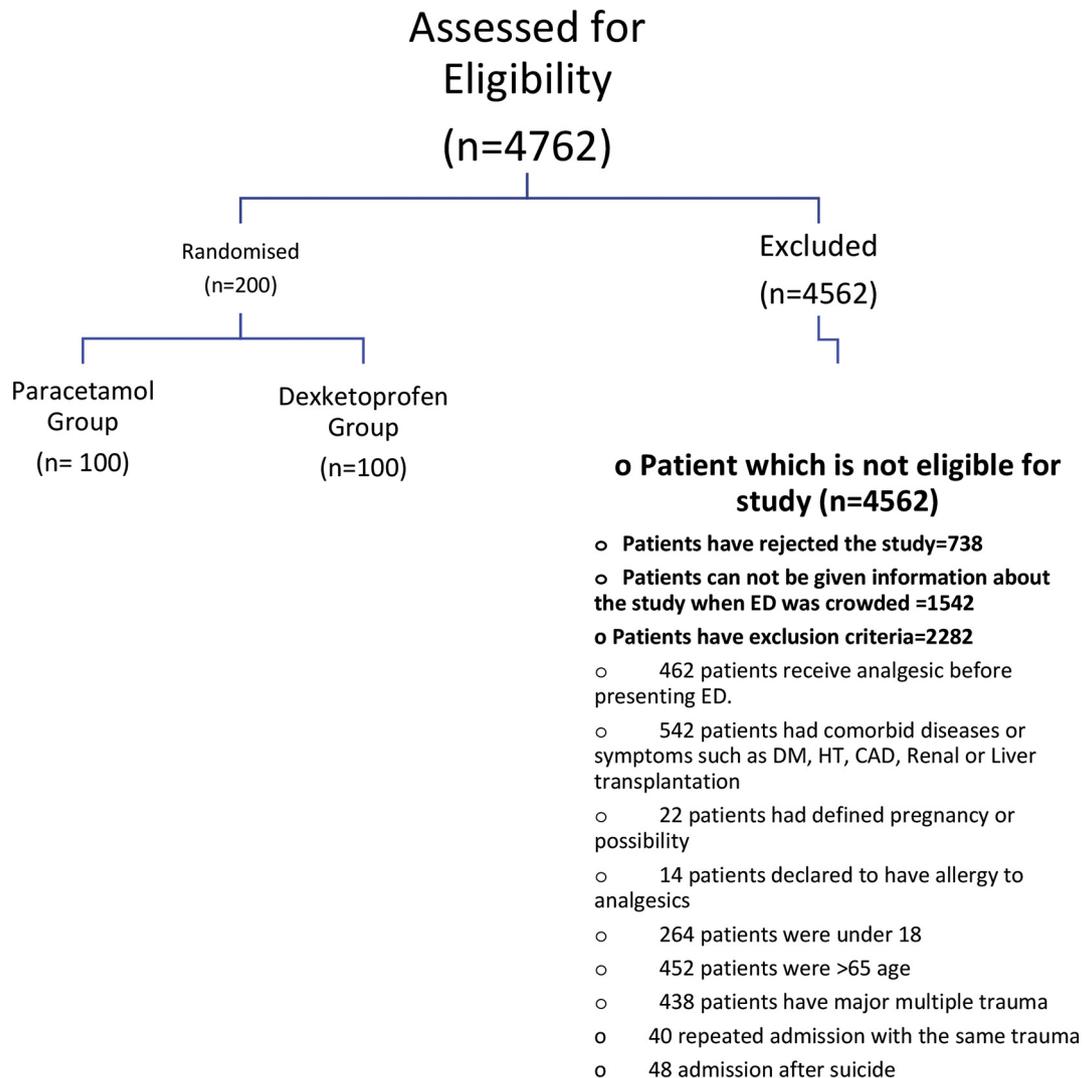
Assessed for Eligibility (n=4762)

Randomised
(n=200)

Excluded
(n=4562)

Paracetamol
Group
(n= 100)

Dexketoprofen
Group
(n=100)

o Patient which is not eligible for study (n=4562)

o **Patients have rejected the study=738**

o **Patients can not be given information about the study when ED was crowded =1542**

o **Patients have exclusion criteria=2282**

o 462 patients receive analgesic before presenting ED.

o 542 patients had comorbid diseases or symptoms such as DM, HT, CAD, Renal or Liver transplantation

o 22 patients had defined pregnancy or possibility

o 14 patients declared to have allergy to analgesics

o 264 patients were under 18

o 452 patients were >65 age

o 438 patients have major multiple trauma

o 40 repeated admission with the same trauma

o 48 admission after suicide

Fig. 1. Flow diagram of eligible patients for study.

the dexketoprofen group. The mean value of the respiratory rate was 17.46 ± 3.44 for the paracetamol group and 17.46 ± 3.64 for the dexketoprofen group. The mean value of the body temperature was 36.54 ± 0.26 for the paracetamol group and 36.53 ± 0.26 for the dexketoprofen group (Table 1).

There was not a significant difference between paracetamol and dexketoprofen groups in terms of initial NRS pain score (p = 0.054), and no significant difference was found between paracetamol and dexketoprofen groups (p = 0.181) with respect to initial VAS scores.

Paracetamol and dexketoprofen administration seems to have reduced NRS pain scores over the time. At the beginning, while the mean NRS pain score of the paracetamol group was 6.77 ± 1.56, the mean NRS pain score of the dexketoprofen group was 7.21 ± 1.42. At the 15th minute, the pain NRS score in the paracetamol group decreased to 5.39 ± 1.59 and in the dexketoprofen group to 5.81 ± 1.76. At the 30th minute it dropped to 3.74 ± 2.14 in the paracetamol group and to 4.20 ± 2.74 in the dexketoprofen group. Finally, at the 60th minute it fell to 2.58 ± 5.24 in the paracetamol group and to 2.54 ± 2.0 in the

Table 1
Baseline characteristics

Variable	Paracetamol group (n = 100)		Dexketoprofen group (n = 100)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Age	36.75 ± 1.94	34 (24–48)	37.8 ± 15.37	35 (23–50)
Systolic blood pressure	120.37 ± 10.39	120 (113.5–130)	120.63 ± 8.57	120 (115–130)
Diastolic blood pressure	78.98 ± 5.12	80 (80–80)	78.55 ± 5.42	80 (80–80)
Heart rate	78.13 ± 6.13	77.5 (72–84)	78.72 ± 6.99	79 (73–83.5)
Respiratory rate	17.46 ± 3.44	17 (14–20)	17.46 ± 3.64	16 (15–20)
Body temperature	36.54 ± 0.26	36.55 (36.42–36.70)	36.53 ± 0.26	36.5 (36.4–36.7)

IQR interquartile range.
SD standard deviation.
Data reported as mean ± SD and median (IQR).

Table 2
Pain outcome measures of the treatment groups

Variable		Paracetamol group		Dexketoprofen group		p[a]
		Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Visual analogue score	Baseline	70.37 ± 14.62	70 (60–80)	73.61 ± 13.69	73 (63–84.5)	0.181
	15 min	56.63 ± 15.13	60 (50–65)	59.72 ± 17.12	60 (50–70)	0.405
	30 min	36.77 ± 21.05	40 (20.25–53)	41.02 ± 22.14	44 (30–54.25)	0.224
	60 min	21.90 ± 21.87	19 (0–40)	25.76 ± 20.52	25 (10–40)	0.130
	Reduction 0–60th min	48.47 ± 21.55	55 (30–65)	48.85 ± 20.72	50 (30.25–60)	0.613
p[**] value VAS		p = 0.0001		p = 0.0001		
Numeric rating score	Baseline	6.77 ± 1.56	6.5 (6–8)	7.21 ± 1.42	7 (6–8)	0.054
	15 min	5.39 ± 1.59	6 (4.25–6)	5.81 ± 1.76	6 (5–7)	0.145
	30 min	3.74 ± 2.14	4 (2–5)	4.20 ± 2.74	4 (3–5)	0.330
	60 min	2.58 ± 5.24	2 (0–3.75)	2.54 ± 2.00	2 (1–4)	0.120
	Reduction 0–60th min	4.64 ± 1.98	5(3–6)	4.67 ± 2.04	5(3–6)	0.940
p[***] value NRS		p = 0.0001		p = 0.0001		

[**]p value and [***]p value were derivated from Friedman Test (Measure into each groups).
Data reported as mean ± SD and median (IQR).
 [a] p Values were derivated from Mann Whitney *U* test and Independent Samples *t*-Test (Measure Between two groups).

dexketoprofen group (Table 2). There was no statistically significant difference between the paracetamol and dexketoprofen groups in terms of NRS values at 60th minute (p = 0.120) (Table 2) (Fig. 2). Median reduction in NRS score at 60 min was 5 (IQR 3–6) for the paracetamol group and 5 (IQR 3–6) for the dexketoprofen group. There was no statistically significant difference between the paracetamol and dexketoprofen groups in terms of NRS reductions (p = 0.940).

Paracetamol and dexketoprofen administration reduce VAS pain scores over the time. At the beginning, while the mean VAS pain score of the paracetamol group was 70.37 ± 14.62, the mean VAS pain score of the dexketoprofen group was 73.61 ± 13.69. At the fifteenth minute, the pain VAS score in the paracetamol group decreased to 56.63 ± 15.13 and in the dexketoprofen group to 59.72 ± 17.12. At the 30th minute it decreased to 36.77 ± 21.05 in the paracetamol group and to 41.02 ± 22.14 in the dexketoprofen group; at the sixtieth minute it decreased to 21.90 ± 21.87 in the paracetamol group and to 25.76 ± 20.52 in the dexketoprofen group (Table 2). There was no statistically significant difference between the paracetamol and dexketoprofen groups in terms of VAS values at 60th minute (p = 0.130) (Table 2) (Fig. 3). Median

reduction in VAS score at 60 min was 55 (IQR 30–65) for the paracetamol group and 50 (IQR 30.25–60) for the dexketoprofen group. There was no statistically significant difference between the paracetamol and dexketoprofen groups in terms of VAS reductions (p = 0.613).

When the pain intensity of the patients was assessed according to VRS, 37 patients (37%) in the paracetamol group and 57 patients (57%) in the dexketoprofen group reported severe pain at the beginning of the study. At the 60th minute, 1 patient (1%) in the paracetamol group and 1 patient (1%) in the dexketoprofen group reported that their pain remained severe (Table 3).

Paracetamol and dexketoprofen groups were categorized and compared according to VRS score changes. There was a significant difference between two groups at baseline (p = 0.012), but as seen in Fig. 4, there was no significant difference between both groups at 15th, 30th and 60th minute (p = 0.134; p = 0.373; p = 0.555 respectively) (Fig. 4).

13 patients in the paracetamol group and 11 patients in the dexketoprofen group received rescue treatment. However, there was no statistically significant difference between both groups in terms of requirement of the rescue treatment (p = 0.684).
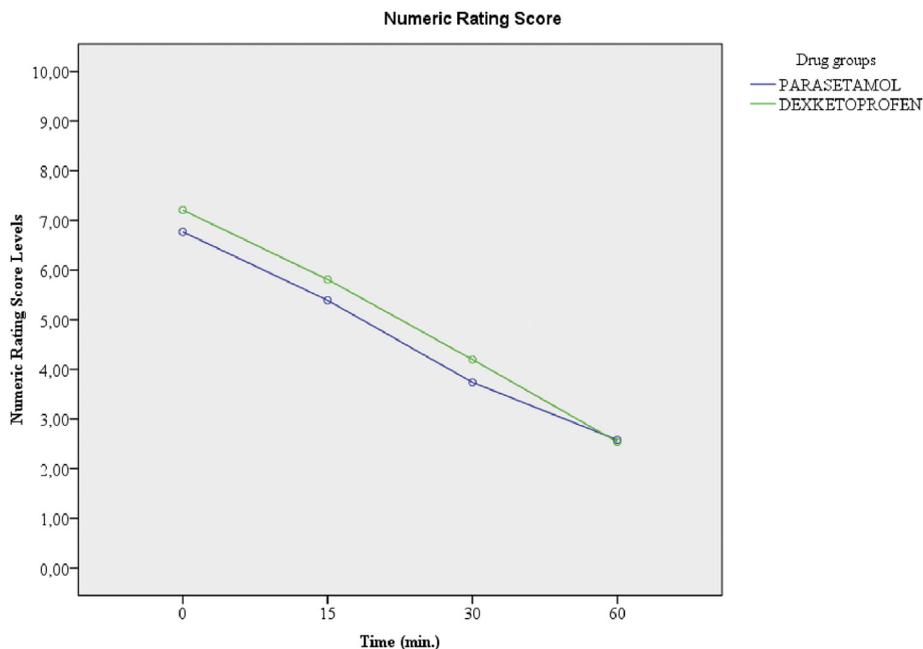

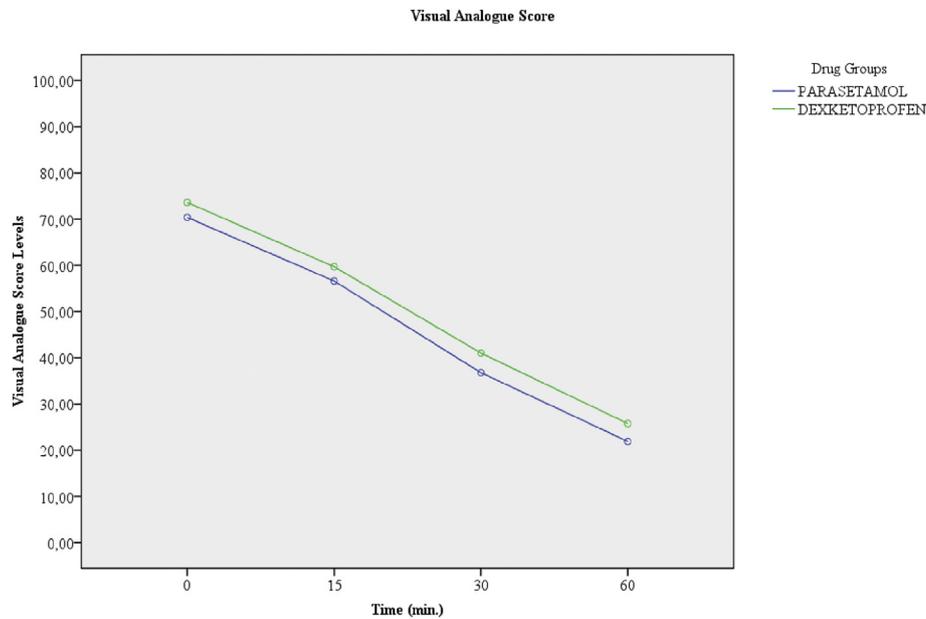**Fig. 2.** Numeric rating scores of the groups.

Visual Analogue Score

Fig. 3. Visual analogue scores of the groups.

4. Discussion

Our prospective, randomised and double-blind study found no statistically significant difference between the groups receiving dexketoprofen and paracetamol for acute pain due to musculoskeletal trauma (p = 0.96). Rescue treatment was provided to 13 patients in the paracetamol group and 11 patients in the dexketoprofen group, which was not statistically significant (p = 0.684), either. Paracetamol and dexketoprofen administration reduced pain VAS, NRS and VRS scores over time. No significant difference was observed between paracetamol and dexketoprofen groups in terms of 0–60 min VAS and NRS exchange (p values = 0.940, p = 0.613, respectively).

In the literature review, we found that paracetamol was often compared with other pain relievers in traumatic or non–traumatic injuries. We observed that paracetamol and other nonsteroidal antiinflammatory drugs were compared in some studies in the form of oral ingestion of the drug [14,15]. In a few studies, IV paracetamol was compared with other IV nonsteroidal drugs and IV opioids [16-19].

In a study conducted by Ridderikhof ML, oral paracetamol was not less effective than oral diclofenac and paracetamol + diclofenac group in traumatic injuries [15]. Moreover, in a double-blind pilot study with 55 patients suffering from traumatic extremity pain who were admitted to the emergency service, Craig et al. demonstrated that IV paracetamol and IV morphine analgesia were equally effective, and that morphine side effects were significantly higher than IV paracetamol group [9]. The studies between 1985 and 2014 were evaluated and meta-analyzed by Jones P. et al. [20]. In this review, low or very low quality but consistent evidence has been obtained showing no significant difference between NSAIDs and paracetamol, opioids or paracetamol and opioid combination in terms of pain or swelling after soft tissue injury. Similar to our study, these studies demonstrate that the effectiveness of paracetamol was found no less than dexketoprofen [19-21].

In the studies investigated in the review by Jones P. et al., in the paracetamol group of 377 patients whose pain was <24 h and followed for one to 2 h, the VAS score average was in the range of 43–55 mm and decreased to 13–19 mm in the basal state, whereas the mean pain score in

Table 3
Verbal rating score outcome measures of the treatment groups

	Paracetamol group	n (%)	Dexketoprofen group	n (%)	p Value
Baseline	Severe	37(37)	Severe	57(57)	$p^0 = 0.012$
	Moderate	59(59)	Moderate	42(42)	
	Mild	4(4)	Mild	1(1)	
	No Pain	0(0)	No Pain	0(0)	
15 min	Severe	11(11)	Severe	23(23)	$p^1 = 0.134$
	Moderate	64(64)	Moderate	56(56)	
	Mild	23(23)	Mild	18(18)	
	No Pain	2(2)	No Pain	3(3)	
30 min	Severe	2(2)	Severe	7(7)	$p^2 = 0.373$
	Moderate	36(36)	Moderate	37(37)	
	Mild	44(44)	Mild	39(39)	
	No Pain	18(18)	No Pain	17(17)	
60 min	Severe	1(1)	Severe	1(1)	$p^3 = 0.555$
	Moderate	15(15)	Moderate	18(18)	
	Mild	38(38)	Mild	45(45)	
	No Pain	46(46)	No Pain	36(36)	

p values are derivated from Chi-Square Test. It is a comparison the changing of VRS score during 60.
p^0 value is a comparison of the VRS score between groups at baseline.
p^1 value is a comparison of the VRS score between groups 15th minute.
p^2 value is a comparison of the VRS score between groups 30th minute.
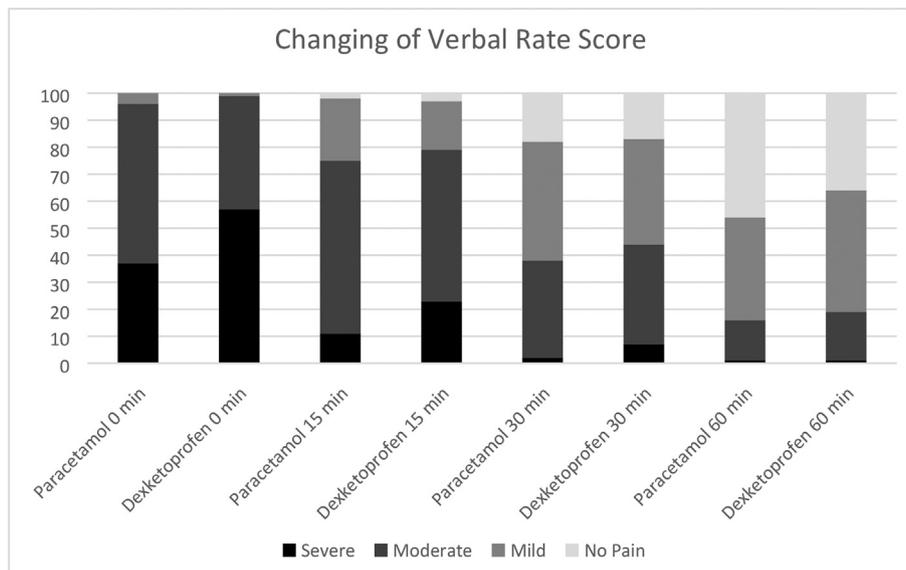p^3 value is a comparison of the VRS score between groups 60th minute.

Fig. 4. Changing of verbal rate scores.

the NSAID group was 1.50 mm higher. There was no statistically significant difference between the two drug groups [20]. Woo et al. compared the efficacy of oral paracetamol (1 g), diclofenac (25 mg) and indomethazine (25 mg) in patients presenting with musculoskeletal trauma, and the decrease in VAS in groups was found to be similar, underlining the fact that NSAIDs, paracetamol, paracetamol + diclofenac combination were equally safe in reducing musculoskeletal pain [21]. In a randomised, double-blind study by Akil et al., who considered the use of paracetamol and dexketoprofen administered intravenously for non-traumatic musculoskeletal pain, similar drug doses — dexketoprofen 50 mg IV for the first group (n = 49), paracetamol 1 g IV for the other group (n = 46) — were applied. When the first-hour VAS scores were compared, no significant difference was found between the drugs on the pain scores as far as the baseline values are concerned [19]. Similar to these studies, our study demonstrates that the decrease in VAS in the paracetamol group was found no less than the dexketoprofen group [19-21]. In our study, the beginning and 60th minute VAS values of dexketoprofen group were significantly higher than the paracetamol group (Table 1). However, there was no significant difference between the two groups in terms of VAS value reduction (p = 0.613).

In our study, the change of VAS value between 0 and 60 min in two groups was similar with a minimal excess in favor of dexketoprofen (ΔVAS Paracetamol: 67.79, ΔVAS Dexketoprofen: 68.53) (p = 0.96). In a study by Bondarsky et al. with 30 patients admitted to the emergency department with a musculoskeletal pain, the VAS in the oral paracetamol, ibuprofen and ibuprofen + paracetamol groups was established as 20 mm less than the baseline, and there was no difference between the groups [14]. The VAS change in our study was much higher than the Bondarsky et al.'s study, suggesting that IV administration of drugs might be the reason for the greater VAS change in our study.

In the study conducted by Ridderikhof et al., the NRS scores of the groups were compared, and at the end of 90 min patients had clinical relief at rest in the oral paracetamol group [15]. In a double-blind, randomised controlled study involving 200 patients conducted by Demirozogul et al., the efficacy of IV paracetamol (1 g) and IV dexketoprofen (50 mg) was compared in patients presenting with nontraumatic musculoskeletal system pain to an emergency service [22]. When the 0–15–30–60 min NRS scores of these patients were examined, it was observed that the NRS scores decreased significantly in both groups (p < 0.001). Nevertheless, there was no statistically

significant difference between paracetamol and dexetoprofen groups in terms of NRS change at 0–15–30-60 min (0 min p = 0.184; 15 min p = 0.531; 30 min p = 0.181; 60 min p = 0.061) [22]. In a similar vein, NRS scores in our study decreased to about 1/3 between 0 and 60 min. Both groups had a significant NRS score change between 0 and 60 min, though no statistically significant difference was found between the NRS score changes among the groups. Paracetamol group and dexetoprofen group had equivalent NRS score change, and paracetamol was as effective as dexetoprofen in reducing pain.

In Demirozogul et al.'s study, the change in VRS score in both groups was examined at 0–60 min, and the ratio of patients with severe pain of 81% in the paracetamol group and 88% in the dexetoprofen group dropped to 3% and 2% respectively, yet there was no significant difference between both groups (0 min p = 0.171; 15 min p = 0.550; 30 min p = 0.211; 60 min p = 0.329) [21]. In our study, at the end of 60 min, the severely painful patients' ratio decreased from 37% to 1% in the paracetamol group and from 57% to 1% in the dexetoprofen group according to the VRS scores, although the decrease in the VRS scores of each group was similar (p = 0.482). Similar to Demirozogul et al.'s study, paracetamol and dexetoprofen reduced the VRS score equally.

4.1. Limitations

There are some limitations to this study. As this was a single-center study with a small sample size, our local data and results may not be representative in other settings or institutions with different patient populations. There is no follow-up data of the study patients as to whether their pain recurred or they attended another medical facility because of their traumatic musculoskeletal pain. This trial did not assess mood, quality of life, or return to work, which are important outcomes of pain management. Additional studies are warranted to define the effects of adequate analgesia on these endpoints in patients with acute musculoskeletal pain both during and after the ED visit.

5. Conclusion

The effectiveness of IV paracetamol treatment in patients presenting with acute musculoskeletal trauma in the emergency department was similar to that of IV dexketoprofen treatment in reducing pain severity.

Conflict of interest statement

The authors declare that they have no conflicts of interests.

Acknowledgment

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