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# Intravenous dexketoprofen versus paracetamol in non-traumatic musculoskeletal pain in the emergency department: A randomized clinical trial <sup>☆</sup>

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## ABSTRACT

**Introduction:** Although acute musculoskeletal pain has a wide range of causes from tendinitis, muscle spasm, to bone and joint injuries, it is a frequent occurrence in emergency services. Paracetamol and non-steroidal anti-inflammatory analgesics (NSAID) are common used in the treatment of musculoskeletal pain. This study sets out to compare the effectiveness of intravenous dexketoprofen and paracetamol in musculoskeletal pain relief.

**Methods:** This prospective, randomized, double blind, controlled study was carried out in a university emergency room. The participating patients were randomized 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) was employed for pain measurement at baseline, after 15, after 30 and after 60 mins.

**Results:** 200 patients were included in the study, excluding 7342 of them. The mean age of the patients was calculated as 32,6. Paracetamol and dexketoprofen intervention decreases NRS pain scores over time. When compared to all pain locations, the NRS pain score of the patients was found to be statistically more effective in dexketoprofen than in paracetamol ( $p = 0.001$ ). Paracetamol and dexketoprofen intervention reduces pain VAS scores over time. When the VAS pain score of the patients was compared to all pain locations, dexketoprofen was found to be statistically more effective than paracetamol ( $p = 0.001$ ).

**Conclusion:** Intravenous dexketoprofen seemed to achieve superior analgesia to intravenous paracetamol when compared with all pain locations in patients with non-traumatic musculoskeletal pain.

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## 1. Introduction

Although acute musculoskeletal pain has a wide range of causes from tendinitis, muscle spasm, to bone and joint injuries, it is a frequent occurrence in emergency services. Most musculoskeletal problems are the ones which are short-term, self-limiting or can be dealt with simple analgesia and/or physical therapy such as physiotherapy or osteopathy. Acute pain does not require long-term treatment with analgesic drugs, which can be instrumental in relieving pain and improving function. The most commonly used analgesic drugs are oral and topical

nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol and opioids [1].

The principal goal of emergency analgesic treatment is to alleviate the pain rapidly, with minimized adverse effects and with no recurrence after discharge, and pain treatment is crucial at this point [2,3]. The preferred course of treatment, in this context, includes medications with the least contraindications and the most powerful pain-relieving activity. Non-steroidal anti-inflammatory analgesics (NSAIDs) and paracetamol, though with their inherent side effects, are often preferred in the management of musculoskeletal pain [1,2]. Dexketoprofen too is a drug within the NSAIDs category. While opioids pave the way for quick and effective pain relief, they also produce adverse effects, such as nausea, vomiting, dizziness, and hypotension [4]. With the introduction of parenteral forms of NSAIDs into the market, researchers have recently devoted close attention to their analgesic effectiveness

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[5,6]. Notably the intravenous (IV) form of paracetamol is a more recent approach than other NSAIDs, and not only is its margin of safety large, but its adverse effects also show low incidence. The paracetamol IV form has proved to be effective, yet researchers still hope to obtain conclusive evidence as to whether it is a safe substitute for other analgesics [7–9]. Although the paracetamol IV form is diffused into the body faster than its oral counterpart and so facilitates discharge and lowers the monitoring time in busy emergency wards [11], both drugs are often administered in the management of musculoskeletal pain in emergency departments (ED) [1,10].

This study sets out to compare the effectiveness of intravenous dexametopfen and paracetamol in musculoskeletal pain relief. The established hypothesis here is that, when compared to dexametopfen, paracetamol is not a substandard medication in the treatment of musculoskeletal pain and can diminish both the use of NSAIDs and their side effects.

## 2. Methods

### 2.1. Study type

Our study, which is actually an equivalence study, was approved by Pamukkale University Ethical Committee for Clinical Investigations with the decision number 2015/09 dated 14 May 2015. The study was registered and approved by the American clinical trial registry (NCT03122314 at <https://clinicaltrials.gov>).

### 2.2. Study population

The current study consisted of the patients who were admitted into emergency service owing to non-traumatic musculoskeletal system pain and gave their consent to take part in the study. The patients in this study were selected according to specific inclusion and exclusion measures. The study was carried out between 31 August 2015 and 01 September 2016, at ED, Pamukkale University, Denizli, Turkey.

### 2.3. Subject selection

The inclusion criteria for recruiting the relevant participants was the complaint of isolated non-traumatic musculoskeletal pain, a VAS pain score of 50 mm and above, moderate-severe pain, being 18 years old and older but younger than 65 years old, and the consent to participate in the study (females with reproductive potential and on the contraceptives were included, too).

On the other hand, the exclusion criteria were the lack of consent to participate, absence of information about the study because ED was too busy, taking analgesics before presenting ED, suffering from comorbid diseases or symptoms like diabetes mellitus, hypertension, coronary artery disease, renal or liver transplantation, having defined pregnancy or possibility and breast-feeding, having allergy to analgesics, being under 18 or > 65 age, undergoing major multiple trauma and applying to ED continually with the same trauma or following a suicide attempt, experiencing neurological deficits, suffering from sciatica and back pain, having cardiac chest pain, having chronic pain, suffering from pre-existing dexametopfen and paracetamol-induced gastrointestinal bleeding and perforation, having reflected pain, and having neoplastic pain.

### 2.4. Research protocol

Upon presenting to emergency service, the initial examinations of all the non-traumatic patients were carried out immediately. VAS pain scores were measured and logged by the examining

physician as the standard procedure during the examination. The study followed a simple randomisation method. An assistant doctor, blind to the study, worked out the randomisation schedule with a computer. After a physician outside the study collected the informed consent, the eligible patients were assigned a study number placed in a sealed envelope. Merely this person had knowledge of the study numbers and the matching drugs till the end of the study.

The study groups and dosages administered were as follows:

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

Group 2: Dexametopfen (50 mg) (Arvels, IE Ulagay-Menarini, Turkey); 50 mg in 150 ml normal saline.

While one nurse from the emergency service was responsible for preparing the study drug, the other one to whom the drugs used in the study were unknown was responsible for administering the study drug. The formerly assigned numbers kept in opaque envelopes were opened by the nurse who prepared the study drug. The patients meeting the inclusion criteria were directed to the ward called monitored observation unit in the ED, where they were monitored and their vascular accesses were established. The calibration of the study drugs were performed by the nurse in charge in ED, while their administration was carried out by the other nurse. The drugs calibrated for both groups were seen-through and the same in appearance.

After the study drug was randomized, 150 ml of saline was used for its dilution, and it was injected as an IV fast infusion. The pain intensity was measured through NRS and VAS at 0th, 15th, 30th, and 60th minutes and was logged by the examining doctor. The patients were screened in case of any critical adverse effects during this period. The study was stopped at the 60th minute, and when the patients complained about progressing pain (VAS pain score of 50 mm and above), they were injected with 1 µg/kg of fentanyl as a rescue therapy. Fentanyl (Talinat), compensated by the research budget, was sent for from the hospital pharmacy with a red prescription. No further painkiller was administered in this study, apart from the aforementioned drugs. The preparation of the drugs exploited in the study followed the guidelines in 'Good Manufacturing Practices'.

### 2.5. Data analysis

The data collected were analyzed in Statistical Package for Social Sciences 22.0 (IBM Corp., SPSS Inc., Chicago IL, USA). Considering that the difference between both groups could produce low effect size ( $d_z = 0.3$ ), we conducted a power analysis before embarking on the study. Therefore, the inclusion of 97 participants in the study would lead to 90% power within 95% confidence level. Accordingly, this study consisted of 100 participants for Paracetamol group and 100 for Dexametopfen group. In terms of VAS results, 100% power within 95% confidence was achieved for both drugs (par  $d_z = 3,95$ , dex  $d_z = 4,59$ ). The descriptive statistics were presented as mean and standard deviation, whereas the averages were provided as mean ± standard deviation. Independent groups were analyzed by using chi-square and Mann–Whitney *U* test for non-normal distribution. Kolmogorov–Smirnov test was carried out to analyze the normality of the dataset. In statistically repetitive measurements (musculoskeletal pain VAS, NRS scores), the groups were compared, using the Friedman Test. Statistical significance level was set as  $p < 0,05$  for all analyzes, as in most studies.

## 3. Results

During the study period, XXXXXX University Adult Emergency Department admitted a total of 94,888 patients, 7542 of whom

presented with musculoskeletal pain. Afterwards, 200 patients were included in the study, excluding 7342 of them (Fig. 1). While 96 (48%) of the patients were female, 104 (52%) were male. The mean age was 32.6. 37 patients (18.5%) reported pain complaints in their neck, 37 (18.5%) in shoulder, 63 (31.5%) in back, and 63 (31.5%) in hip and knee.

No statistically significant difference was found between dexketoprofen and paracetamol groups in terms of gender ( $p = 0.777$ ), pain location ( $p = 0.773$ ) and mean age ( $p = 0.161$ ).

Paracetamol and dexketoprofen intervention decreases NRS pain scores over time. The NRS pain score of the initial paracetamol and dexketoprofen group was  $7.9 \pm 1.1$ ,  $8.1 \pm 1.0$ , respectively. At the 60th minute, it fell to  $1.7 \pm 1.9$  in the paracetamol group and  $1.3 \pm 1.7$  in the dexketoprofen group (Table 1).

When compared to all pain locations, the NRS pain score of the patients was found to be statistically more effective in dexketoprofen than in paracetamol (Fig. 2).

Paracetamol and dexketoprofen intervention reduces pain VAS scores over time, and time-dependent changes bear a resemblance in the graph. The initial pain VAS score of the paracetamol group was  $8.2 \pm 1.0$ , while that of the dexketoprofen group was  $8.1 \pm 1.0$ . This score decreased to  $1.7 \pm 1.9$  in the paracetamol group and  $1.3 \pm 1.7$  in the dexketoprofen group (Table 2).

When the VAS pain score of the patients was compared to all pain locations, dexketoprofen was found to be statistically more effective than paracetamol between 0 and 30 min and between 0 and 60 min (Fig. 3).

**Table 1**

Time-dependent change in NRS scores of musculoskeletal pain in groups.

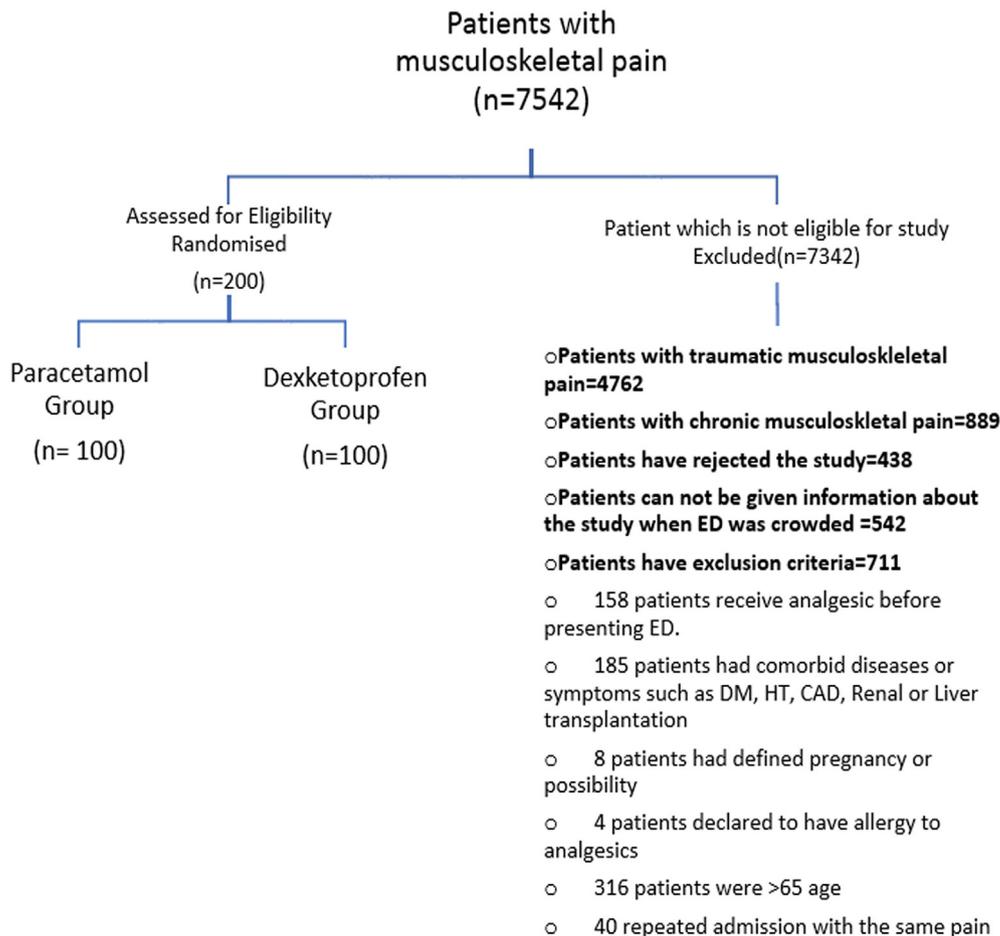
NRS pain scores mean $\pm$ ss	Paracetamol	Dexketoprofen	p <sup>*</sup>
NRS 0TH MIN	$7.9 \pm 1.1$	$8.1 \pm 1.0$	0,184
NRS 15TH MIN	$5.9 \pm 1.5$	$5.7 \pm 1.5$	0,531
NRS 30TH MIN	$3.9 \pm 1.9$	$3.6 \pm 1.8$	0,181
NRS 60TH MIN	$1.7 \pm 1.9$	$1.3 \pm 1.7$	0,061
p <sup>**</sup>	<0,001	<0,001	

\* p values were derivated from Mann Whitney U test.

\*\* p values were derivated from Friedman test.

6 patients in the dexketoprofen group and 12 in paracetamol group whose VAS pain scores reached 50 mm and more at the 60th minute were injected with fentanyl  $1 \mu\text{g}/\text{kg}$ . Moreover, VAS changes in the musculoskeletal pain at the 60th minute were calculated as  $6.44 \pm 1.71$  in the paracetamol group and  $7.09 \pm 1.44$  in the dexketoprofen group. On the other hand, NRS changes in the musculoskeletal pain at the 60th minute were found to be  $6.16 \pm 1.68$  in the paracetamol group and  $6.85 \pm 1.47$  in the dexketoprofen group (Table 3).

There was no statistically significant difference between paracetamol and dexketoprofen in terms of their efficacy in neck pain, shoulder pain, hip and knee pain ( $p = 0.323$ ,  $p = 0.169$ ,  $p = 0.089$ , respectively, and p values were derived from Mann Whitney U test) but in patients with back pain there was a significant difference between paracetamol and dexketoprofen ( $p = 0.043$ , and p value was derived from Mann Whitney U test) (Fig. 4).



**Fig. 1.** Flow chart.

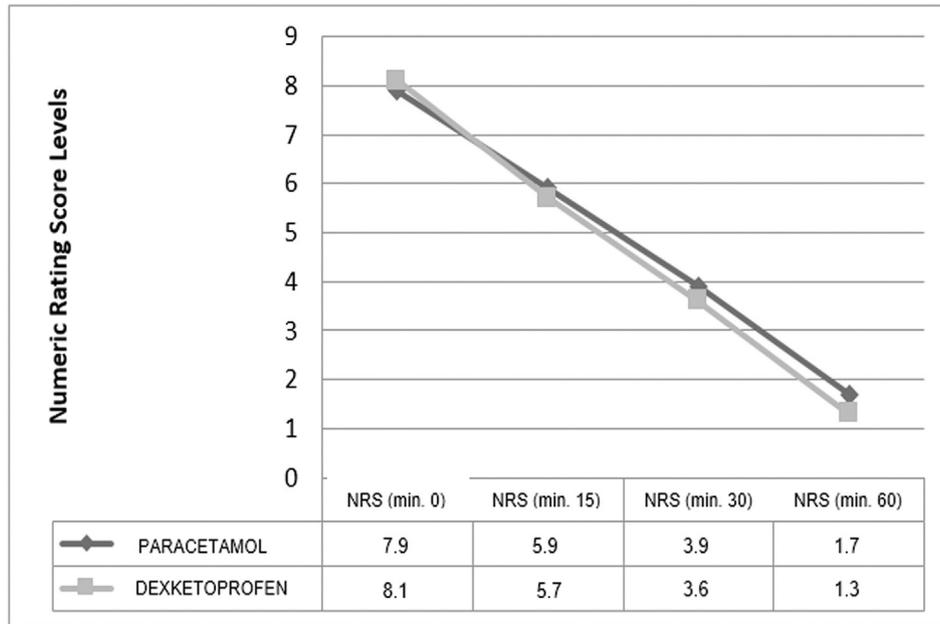


Fig. 2. Numeric rating scores of the groups.

**Table 2**  
Time-dependent change in VAS scores of musculoskeletal pain in groups

VAS pain scores mean ± ss	Paracetamol	Dexketoprofen	p <sup>*</sup>
VAS 0TH MIN	8.2 ± 1.0	8.1 ± 1.0	0.324
VAS 15TH MIN	6.0 ± 1.6	5.9 ± 1.5	0.494
VAS 30TH MIN	3.9 ± 1.8	3.6 ± 1.8	0.112
VAS 60TH MIN	1.7 ± 1.9	1.3 ± 1.7	0.059
p <sup>**</sup>	<0.001	<0.001	

\* p values were derivated from Mann Whitney U test.

\*\* p values were derivated from Friedman test.

**Table 3**  
Treatment efficacy for groups

Parameters	Paracetamol	Dexketoprofen	p
Relief Therapy (n)	12	6	*0.217
VAS changes in the musculoskeletal pain at the 60th minute (mean ± SD)	6.44 ± 1.71	7.09 ± 1.44	**0.001
NRS changes in the musculoskeletal pain at the 60th minute (mean ± SD)	6.16 ± 1.68	6.85 ± 1.47	**0.001

\* p values are derivated from Chi-Square Test.

\*\* p value was derivated from Mann Whitney U test.

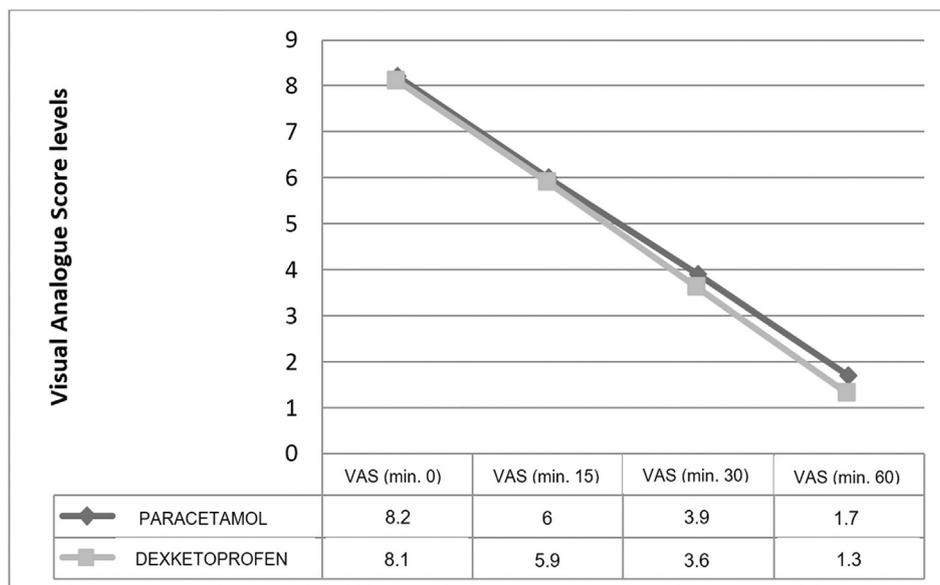


Fig. 3. Visual analogue scores of the groups.

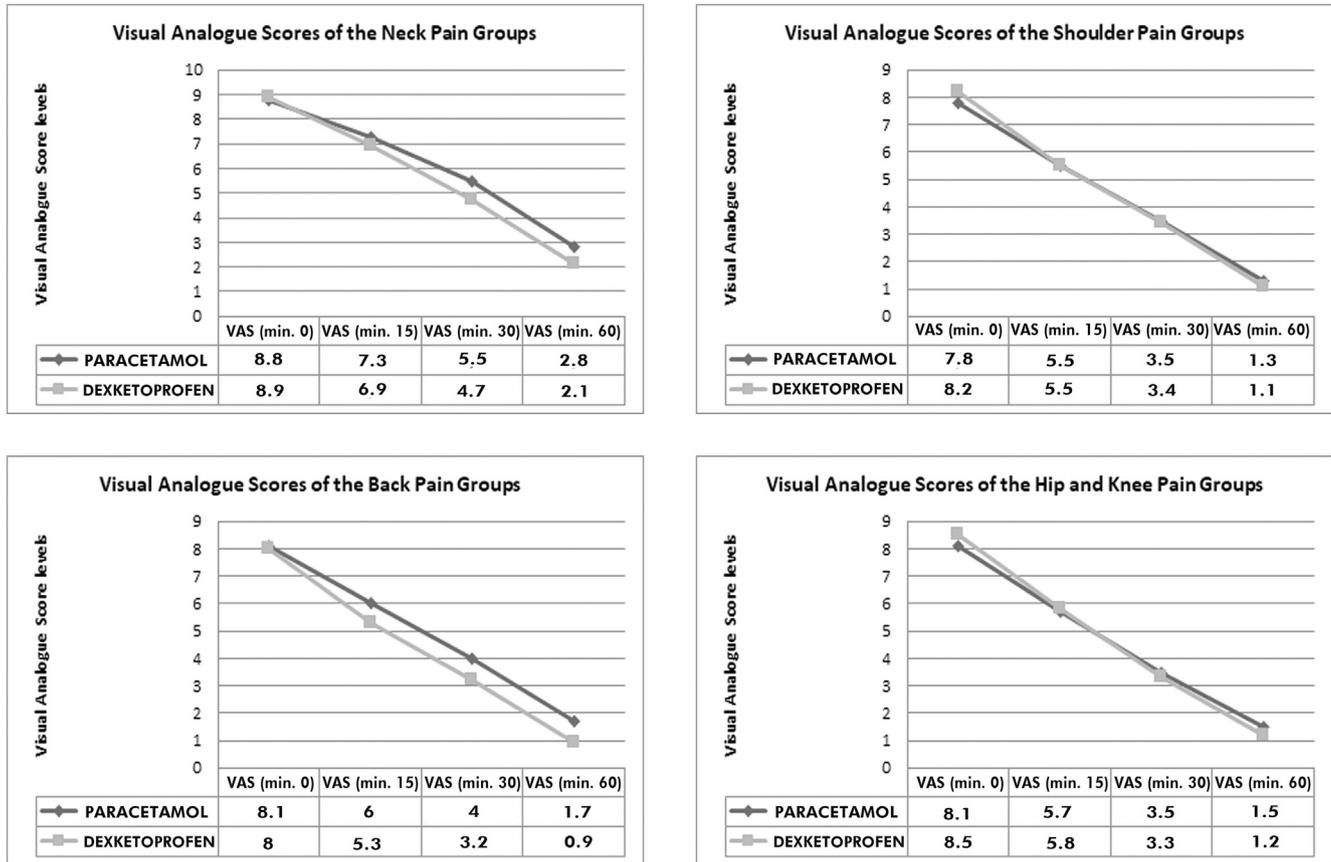


Fig. 4. Visual analogue scores of the neck, shoulder, back, hip and knee pain groups.

**4. Discussion**

In our study, we compared the effectiveness of paracetamol and dexametopfen in acute musculoskeletal pain not caused by trauma within the ED. Since we are of the opinion that parenteral treatment in the ED is more comfortable, effective and faster for the patient, we conducted our study intravenously, contrary to many oral treatment studies in the literature. At the 30th minute on average, the pain VAS score of most of our patients fell below 5 and they left the ED with pleasure. As far as VAS and NRS scores in each treatment group are concerned, dexametopfen outclassed paracetamol in analgesic efficiency, when the 0th–60th minutes were compared. In addition, when the efficacy of paracetamol and dexametopfen in the neck, shoulder, back and hip-knee pains were compared, no superiority of the one over the other emerged. To the best of our knowledge, our study is the first one to compare the effectiveness of IV paracetamol and dexametopfen in musculoskeletal pain in the ED.

In a randomized, double-blind and controlled study, Eric et al. [12] compared the efficacy of 1 g oral paracetamol (n = 30), 800 mg oral ibuprofen (n = 30) and a combination of both (n = 30) in musculoskeletal pain in the ED. Pain scores across the groups were compared with the VAS pain scale at the 20th, 40th, and 60th minutes. The initial pain score was 59 for ibuprofen; 61 for paracetamol and 62 for the combination of both, and it was reported that each group significantly reduced their pain one hour after the drug administration (p = 0.001). The need for salvage drugs was similar between the groups.

Comparing 1 mg of paracetamol (n = 100) and 50 mg dexametopfen (n = 100) in acute musculoskeletal trauma, Yilmaz et al. [13] reported that paracetamol and dexametopfen administration

lowered VAS pain scores in the course of time. Besides, the administration of these drugs equally brought about pain relief for acute musculoskeletal trauma.

In a randomized, double-blind and controlled study, William et al. [14] compared the efficacy of oral 1 g paracetamol (n = 66) and oral 25 mg indomethacin (n = 69), 25 mg diclofenac (n = 71) and 1 g paracetamol and 25 mg diclofenac (n = 94) in post-traumatic musculoskeletal pain. VAS pain scores of the patients were measured at 30th, 60th, 90th and 120th minutes. As a result, there was no statistically significant difference in pain relief across the combination groups.

In a randomized, double-blind, prospective, controlled study, Leman et al. [5] investigated the analgesic effectiveness of oral 50 mg sodium diclofenac (n = 57) and 25 mg oral dexametopfen (n = 65) in patients with lower extremity injury. While the mean pain scores were initially equivalent, the mean pain score in the dexametopfen group decreased faster than the diclofenac group during the following 60 min. Five patients in the diclofenac group and three in the dexametopfen group were given salvage drugs. In conclusion, dexametopfen was found to be an effective analgesic, which is compatible with our study.

In a cross-sectional, observational, prospective and cohort study, Buccelletti et al. [15] compared 1000 mg/60 mg paracetamol-codeine (n = 87) and 15 mg ketorolac (n = 113) in localized trauma or inflammatory extremity pain in the ED. The researchers concluded that paracetamol-codeine is equivalent to ketorolac in non-traumatic pain and achieved superior analgesia in acute, muscle and fracture pains.

In a randomized, double-blind, multi-center study, Innes et al. [16] explored the effectiveness of 10 mg ketorolac (n = 63) and 600 mg paracetamol/60 mg codeine (n = 60) for acute low back

pain by using pain intensity on categorical scale and VAS score. In both drug groups, pain relief was observed within the first hour, while the peak effect was reached at 2.2nd hour. No difference existed between the two groups in terms of analgesic efficiency and functional capacity.

When the studies in the literature are analyzed, paracetamol and dexketoprofen are frequently preferred in post-operative pain control.

Koçum et al. [17] compared the analgesic efficacy of IV 1000 mg paracetamol and 50 mg dexketoprofen trometamol in the treatment of postoperative pain in 114 patients undergoing operative hysteroscopy. In operative hysteroscopy, dexketoprofen turned out to be more effective for postoperative analgesia than paracetamol and placebo. The results revealed that opioid need was significantly lower in dexketoprofen group than in paracetamol and control group.

In a randomized, double-blind study, Akil et al. [18] compared the efficacy of IV 50 mg dexketoprofen with IV 1000 mg paracetamol (group 2) after episiotomy. Similar to our study, there was no difference in pain scores according to the baseline values when the first hour VAS scores were compared.

In their study, Gülhaş et al. [19] compared the effectiveness of 50 mg dexketoprofen trometamol, 8 mg lornoxicam and 1 g paracetamol IV forms on post-operative pain in 120 patients undergoing abdominal hysterectomy. The VAS scores of the groups were similar in all evaluation times. It was reported that postoperative dexketoprofen trometamol, paracetamol, and lornoxicam IV forms similarly reduced fentanyl consumption.

In a double-blind, prospective, placebo-controlled randomized study, Unal et al. [20] evaluated the analgesic efficacy and opioid-dependent side effects of the combination of IV paracetamol and dexketoprofen with morphine after abdominal hysterectomy ( $n = 60$ ). The authors concluded that dexketoprofen and paracetamol did not bring about any difference in pain scores and increased the patients' comfort.

Kelsaka et al. [21] investigated the postoperative analgesic effect of IV 50 mg dexketoprofen, administered as preemptive single dose, on the cases where lumbar microdiscectomy are performed. It was concluded that IV dexketoprofen, administered as preemptive single dose, created a post-operative analgesic effect, notably in the first 8 h, on the patients who underwent lumbar microdiscectomy, thereby decreasing total tramadol consumption.

In a randomized, double-blind, placebo-controlled trial, Kesimci et al. [22] aimed to have an insight into the effect of dexketoprofen trometamol and paracetamol, administered as single dose before surgery, on postoperative pain and opioid consumption in a 24-h period after laminectomy. There was no significant difference in mean VAS scores between the groups ( $p > 0.05$ ). The researchers reached the conclusion that the administration of preemptive 25 mg dexketoprofen trometamol in elective lumbar disc surgeries achieved up to 35% decrease in postoperative morphine consumption compared to placebo, but paracetamol did not show the expected effectiveness in this respect.

In a prospective, double-blind, placebo-controlled study design, Tunalı et al. [23] explored the analgesic efficacy of 1 g IV paracetamol and 50 mg IV dexketoprofen after lumbar disc surgery. When compared to the control group, the pain score proved lower in the dexketoprofen group ( $p = 0.01$ ).

Sivriköz et al. [24] studied the postoperative analgesic efficacy of 50 mg dexketoprofen and 8 mg lornoxicam used after a major orthopedic surgery and its contribution to decrease in morphine consumption. The results revealed that administering two doses of 50 mg dexketoprofen and 8 mg lornoxicam per day intravenously provided better analgesia and lower morphine consumption than placebo.

In a randomized, double-blind study, Khalili et al. [25] investigated the comparison of IV 15 mg/kg paracetamol, IM 0.4 mg/kg piroxicam, the combination of both drugs and placebo comparison in the treatment of pain after upper extremity orthopedics surgery. The findings demonstrated that the paracetamol + piroxicam group and the paracetamol-only group significantly decreased pain compared to the other groups.

In their ERCP trial with sedoanalgesia, Akıncı et al. [26] observed that parenteral IV 50 mg dexketoprofen given before the procedure provided better pain control without affecting the recovery process than IV 1 g paracetamol and control group, thus reducing the need for narcotic analgesic and the frequency of undesirable side effects.

In a prospective, double-blind, randomized, controlled trial, Turkcuer et al. [27] compared the efficacy of intravenous 1000 mg paracetamol and 50 mg dexketoprofen in patients applying to the ED with complaints of acute migraine attack. They reported that IV paracetamol and dexketoprofen provided equal efficacy in pain control of the migraine attack in the ED.

Hunold et al. [28] conducted a cross-sectional study on the side effects of oral opioid intake for adults during the first week of acute musculoskeletal pain treatment. The incidence of opioid-related side effects in musculoskeletal pain in the elderly was so high that the drug was reported to be discontinued. As a result, paracetamol and NSAIDs should primarily be given to patients with musculoskeletal pain in the ED. We are of the opinion that opioid should be considered the last resort because of its side effect profile.

## 5. Conclusion

The administration of paracetamol and dexketoprofen reduced pain VAS scores over time, but VAS changes in the musculoskeletal pain between 0th and 60th minutes were found to be  $6.94 \pm 1.71$  in the paracetamol group and  $7.09 \pm 1.44$  in the dexketoprofen group ( $p = 0.001$ ). Besides, dexketoprofen seemed to achieve superior analgesia to paracetamol when compared with all pain locations.

## Conflict of interest statement

None declared.

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## Ethics approval statements

Our study, which is actually an equivalence study, was approved by Pamukkale University Ethical Committee for Clinical Investigations with the decision number 2015/09 dated 14 May 2015.

## Clinical trial registration

([ClinicalTrials.gov](https://clinicaltrials.gov) ID: NCT03122314).

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