American Journal of Emergency Medicine 50 (2021) 142–147

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Comparing two doses of intramuscular ketorolac for treatment of acute musculoskeletal pain in a military emergency department

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ARTICLE INFO

Article history:
Received 17 June 2021
Received in revised form 26 July 2021
Accepted 26 July 2021
Available online xxxx

Keywords:
Emergency department
Ketorolac
Musculoskeletal
Intramuscular
Analgesia
Pain control
Non-inferiority

ABSTRACT

Study objective: The goal of the study was to assess a low-dose versus a high-dose of intramuscular (IM) ketorolac for non-inferiority in adults with acute MSK pain in an emergency department (ED).
Methods: This was a single-blinded, randomized controlled, non-inferiority trial of adults presenting to an ED with a chief complaint of acute MSK pain. Patients were randomized to either a 15 mg or a 60 mg IM ketorolac dose. The primary outcome was the mean difference of change in pain from baseline to 60-min between the two groups as reported on a 100-mm (mm) visual analog scale (VAS). Secondary outcomes included the mean difference of change in VAS scores at 30-min and the incidence of reported adverse effects associated with the administration of ketorolac.
Results: One hundred ten patients were randomized with 55 in each group. The mean difference in pain between groups at 60-min (0.2 mm [95% CI -8.5–8.7]; $p = .98$) and 30 min (−1.7 mm [95% CI -8.5–5.1; $p = .63$) was less than the predetermined non-inferiority margin of 13 mm. There were no major adverse effects reported. Minor adverse effects were more frequent in the 60 mg group ($n = 9$; 16.4% vs. $n = 1$; 1.8%; $p = .016$) with burning at the injection site being the most commonly reported.
Conclusions: A 15 mg dose of IM ketorolac was found to be non-inferior to a 60 mg dose for acute MSK pain in adults presenting to the ED. Discontinuing the practice of ordering 60 mg doses of IM ketorolac in place of a lower dose for acute MSK pain should be considered.

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1. Introduction

1.1. Background

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) and one of the most commonly used parenteral analgesics in the emergency department (ED) for the treatment of moderate to severe pain [1,2]. Through post-marketing research and clinical use, ketorolac has well known efficacy in a variety of clinical conditions to include renal colic, post-operative pain, cancer-related pain, and musculoskeletal (MSK) pain [1-8].

1.2. Importance

Multiple studies have evaluated the analgesic effect of ketorolac administered by the intravenous (IV) route in various dosages and demonstrated a ceiling dose of 10 mg (mg) [1,3,6]. The recommended single dose for intramuscular (IM) ketorolac is 30 to 60 mg for analgesia and is significantly higher than IV ceiling dose [4]. Knowing the ceiling dose is important in minimizing the known adverse effects of ketorolac including gastrointestinal bleeding, reversible inhibition of platelet aggregation, an increase in cardiovascular effects, and renal impairment [9-12]. While there have been studies evaluating the analgesic efficacy of IM ketorolac for various types of pain, there is no readily available research to date, primarily evaluating ketorolac's efficacy by dose via the IM route for acute MSK pain [5,8].

1.3. Goals of this investigation

The overall goal of the study was to assess the efficacy and adverse effects of low-dose versus high-dose of IM ketorolac. Specifically, the

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https://doi.org/10.1016/j.ajem.2021.07.054
0735-6757/Published by Elsevier Inc.

primary aim was to evaluate a single 15 mg IM dose of ketorolac for analgesic non-inferiority versus a single 60 mg IM dose for the treatment of acute MSK pain in an ED setting. The authors chose 15 mg as the lower dose instead of the previously identified ceiling dose of 10 mg for two reasons. First, we wanted to provide clear data the clinician could use in their practice, knowing that ordering a dose of medication such as 10 mg ketorolac is less feasible when there is a dose readily available in a pre-filled syringe. Second, for ease of conducting the study because ketorolac is manufactured in pre-filled vials of 15 mg and 60 mg doses.

2. Methods

2.1. Study design and setting

United States (U.S.) Army Regional Health Command-Centrals Institutional Review Board approved this randomized controlled study (protocol # C.2019.088). Additionally, the study was registered with clinicaltrials.gov (ID # NCT04763876). This was a single-blinded, randomized controlled non-inferiority trial which followed the guidelines set forth in the 2010 Consolidated Standards of Reporting Trials (CONSORT) Statement [13]. Patients were blinded to the IM dose administered. This study was conducted in the ED of a Defense Health Agency (DHA) facility servicing a range of Department of Defense (DoD) and Veterans Affairs (VA) beneficiaries with an average ED census of over 42,000 encounters since 2017. Approximately 7% of patients seen in this ED are diagnosed with a MSK Internal Classification of Diseases (ICD) code in their medical record.

2.2. Selection of participants

Patients considered for this study were a convenience sample of adults aged 18 to 55 years, who presented for management of acute MSK pain with a reported pain intensity of 20 or greater on a standard 100 mm visual analog scale (VAS) and triaged as an emergency severity index (ESI) category four or five. The attending ED clinician caring for the patient needed to agree that IM ketorolac was an appropriate analgesic for their patient. We defined acute onset as less than 30 days. Exclusion criteria included but was not limited to patients weighing less than 50 kg (110 lbs), pregnant or breast feeding, NSAID allergy or hypersensitivity, any analgesic medication use within 12 h and a history of renal disease, gastrointestinal disease, or a bleeding diathesis. See Table 2 for complete inclusion and exclusion criteria.

A single investigator (*NT*) consented participants into the study. He was not the treating Physician Assistant for any of the study subjects. During the consenting process, participants were informed that they may receive rescue analgesia at any time of the study. The type, dose, and route of rescue analgesia was to be determined by the attending Physician rather than the study design. Patients who received rescue analgesia were planned to be excluded from the data analysis due to a perceived increase in analgesic effect.

2.3. Intervention

Patients were randomized to either a 15 mg IM dose or a 60 mg IM dose and were blinded to the dose administered. Prior to data collection, randomization software was utilized to assign our required sample size of participants to one of the two treatment groups (GraphPad Software, www.graphpad.com/quickcalcs/randomize1.cfm, 2018). Data collection sheets were prefilled with the group assignment, placed in sealed envelopes, and then taken out of a secured container in sequential order after the study subject consented to participate.

Investigators informed the nurse assigned to the participant of the dose to be administered. The nurse drew-up and administered the medication. Investigators verified the dosage of medication prior to administration. Our study was designed as a per-protocol analysis, in which only patients who received the initial dose of ketorolac were included our analysis. Patients that required rescue analgesia would have been excluded from our analysis but no patients required rescue analgesia and thus, did not have any effect on the results.

2.4. Measurements

Participants annotated their pain on a VAS immediately prior to ketorolac administration. The VAS was a non-graduated horizontal scale measuring 100 mm, with the left margin representing “no pain” and the right margin representing “severe pain.” Participants drew a vertical line on the VAS to indicate their perceived pain level. An investigator noted the time of medication administration and assessed the participant's pain level after 30 and 60 min. The VAS measurement was verified by two investigators. Additionally, patients were assessed for objective adverse effects and questioned for any subjective adverse effects due to medication administration. After the 60-min assessment, the patient's participation in the study was complete.

2.5. Outcomes

The primary outcome was the change in VAS pain score 60-min after administering IM ketorolac. Secondary outcomes included the change in VAS score at 30-min and the incidence of reported adverse effects associated with the administration of ketorolac. A post-hoc analyses included assessment of ketorolac pain response by patient characteristics and by location of pain.

2.6. Analysis

Data analysis and sample size calculation was performed using the statistical software SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The primary outcome was tested using a one-sided, two-sample equal-variance *t*-test. To assess the lower dose for a difference in adverse effects, a one-sided z-test for two independent proportions was used. To assess for any differences in VAS scores based on demographic data, a Fisher's exact test was utilized. We report continuous variables as means with standard deviations and ordinal variables as proportions with 95% confidence intervals. Statistical significance was defined as $p < .05$.

A one-tailed equal variances t-test was used to perform a sample size calculation. A minimal clinically relevant difference and non-inferiority margin of 13 mm on the VAS was chosen based on prior studies [6,14]. Bijur et al. found that 13 mm was the point at which subjects annotated at least “a little better” or “a little worse” for change in pain scores [14]. If the difference between the two doses is found to be less than 13 mm, the doses will be considered to be non-inferior. Assessing for a 13 mm difference with a standard deviation of 27 mm calculated a minimum sample size of 110 (55 subjects in each arm) when the power is set at 0.8 with an alpha of 0.05. To account for a potential 10% drop out we obtained permission to recruit up to 122 subjects.

3. Results

3.1. Characteristics of study subjects

From July to December 2020, 175 patients were screened, 65 were excluded, and 110 patients were recruited to participate. All 110

consented and zero withdrew from the trial. The study population was 27% female and had a mean age (SD) of 30.9 [9] (Table 1). The most common reason for exclusion was subjects having taken an analgesic medication within the 12 h of presentation to the ED (Fig. 1). Groups were similar when compared by demographic data and there was normal distribution across the sample. These groups were neck/back, small joint (wrist, finger joints, ankle, and toe joints), large joint (shoulder, elbow, hip, and knee), and other (e.g., muscle belly, rib, and hand/feet). Additionally, the same was considered when determining groups for the duration of pain.

3.2. Main results

At 60 min post administration, those receiving the 15 mg dose had a decrease (SD) in pain from baseline of 29.7 mm (22.5) and those receiving the 60 mg dose had a decrease (SD) in pain from baseline of 29.9 mm (23.1). The study's primary outcome of the mean difference between groups at 60-min post administration was 0.1 mm (95% CI -8.5–8.7; $p = .98$) and was less than the predetermined non-inferiority margin of 13 mm (Table 3, Figs. 2 and 3). Similar results were seen between groups at 30 min post administration with a mean difference of −1.7 mm (95% CI -8.5–5.1; $p = .63$). There were no major adverse effects reported at 60-min. Minor adverse effects were more frequent in the 60 mg group ($n = 9$; 16.4% vs. $n = 1$; 1.8%; $p = .016$) with burning at the injection site being the most commonly reported (Table 1).

Further analyses were conducted to determine if pain reduction at 30 or 60 min differed by age, gender, body weight, duration of pain, or the location of the pain and if so, whether these variables interacted with differences in dosage level. Significant differences in pain reduction were evident for only one variable. Patients who presented with back or neck pain reported statistically significant less pain reduction at 30 min ($p = .02$) and at 60 min ($p = .01$) regardless of IM ketorolac dosage, compared to patients presenting with pain in other locations (Table 4). However, this difference did not meet the minimal clinically relevant difference of 13 mm on the VAS. Two-way analyses of variance were conducted to determine if these results differed by the dosage of IM ketorolac administered. No interaction effects were observed, indicating that a higher dose of IM ketorolac did not reduce patients' back or neck pain to any greater degree than the lower dose.

Table 1
Demographic and clinical characteristics of the sample.

Characteristic		Total sample ($n = 110$)	15 mg ($n = 55$)	60 mg ($n = 55$)
Gender, n (%)				
	Female	30 (27.3)	13 (43)	17 (57)
	Male	80 (72.7)	42 (53)	38 (47)
Age, mean (SD)		30.9 (9)	31.1 (9.5)	30.7 (8.6)
Body weight in kg, mean (SD)		83.7 (16.4)	82.8 (16.5)	84.5 (16.4)
Location of pain, n (%)				
	Back/neck	37 (33.6)	20 (54)	17 (46)
	Small joint[a]	23 (20.9)	13 (57)	10 (43)
	Large joint[b]	24 (21.8)	11 (46)	13 (54)
	Other location[c]	26 (23.7)	11 (42)	15 (58)
Duration of pain, n (%)				
	≤24 h	59 (53.6)	22 (37)	37 (63)
	>24 h	51 (46.4)	33 (65)	18 (35)
VAS pain scores, mean (SD)				
	Pre-treatment	68 (17.9)	69.8 (16.5)	66.3 (19.1)
	At 30-min	49.9 (24)	50.8 (23.9)	48.9 (24.3)
	At 60-min	38.2 (27.2)	40 (27.3)	36.4 (27.1)
Reported adverse effects, n (%)				
	Burning at site of injection	4 (3.6)	0	4 (7.3)
	Fatigue	3 (2.7)	1 (1.8)	2 (3.6)
	Headache	2 (1.8)	0	2 (2.6)
	Nausea	1 (0.9)	0	1 (1.8)
	Total	9 (8.2)	1 (1.8)	9 (16.4)[d]

[a] Wrist, finger joints, ankle, and toe joints.
[b] Shoulder, elbow, hip, and knee.
[c] e.g., muscle belly, rib, and hand/feet.
[d] $p = 0.16$.

Table 2
Inclusion and exclusion criteria.

Inclusion criteria
Age 18–55 years of age
DoD or VA beneficiary
ESI 4 or 5
Presenting to WBAMC ED for management of musculoskeletal pain (i.e., general muscular, neck, back, shoulder, arm, forearm, elbow, wrist, finger, hip, knee, thigh, leg, ankle, foot or digits)
Pain intensity of 20 mm or greater on 100 mm VAS
Pain duration less than 30 days
Attending provider concurs with IM ketorolac for analgesia
Exclusion criteria
Body weight less than 50 kg
Pregnant or breast feeding
History of: confirmed, unconfirmed, known, unknown, or suspected peptic ulcer disease, intestinal hemorrhage, renal insufficiency, hepatic insufficiency, cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, dark stools, bright red blood per rectum, hemoptysis, easy bruising, or high risk of bleeding
Unable to confidently convey or unknown medical history
Systolic blood pressure < 90 or > 180 mmHg; pulse rate < 50 or > 150 beats/min
Allergy or hypersensitivity to nonsteroidal anti-inflammatory drugs or Aspirin
Advised by any medical provider to not receive NSAIDs
Any over-the-counter or prescribed opioid and/or non-opioid analgesic medication (oral, per rectum, topical or parenteral) taken within 12 h of ED presentation
Currently taking anticoagulant medications
Concurrent use of medications which are contraindicated with concomitant NSAID use (including but not limited to aspirin, probenecid and pentoxifylline)
Refusal to remain in the WBAMC ED for up to 60 min after injection of ketorolac

4. Discussion

For the primary outcome of pain relief at 60 min, 15 mg of IM ketorolac was non-inferior to 60 mg for adults presenting to the ED with acute MSK pain. None of the subjects required rescue analgesia or left the study due to inadequate pain control. To the authors' knowledge, this is the first study to assess two different doses of IM ketorolac for non-inferiority in the treatment of undifferentiated acute MSK pain in adults presenting to the ED. Our study most closely followed the design of a previous study by Motov et al. evaluating IV ketorolac at three different doses [6]. Contrary to the Motov et al. study, we administered IM ketorolac and solely evaluated it for treatment for MSK pain, while they evaluated IV ketorolac in the treatment of undifferentiated acute moderate to severe pain. Additionally, we compared two doses of ketorolac (15 mg and 60 mg), where Motov et al. compared three doses (10 mg, 15 mg, 30 mg). Two previous studies evaluated different doses of IM ketorolac for the treatment of cancer and found no statistically significant difference between the compared doses, supporting the efficacy of a lower dose of IM ketorolac. Brown and colleagues published another study showing no statistically significant difference in compared doses of IV ketorolac for the treatment of postoperative pain [10]. Similar to these studies, we found a lower dose of IM ketorolac was non-inferior for pain management. While these previous studies support the use of lower dose ketorolac for undifferentiated acute pain, cancer pain, and postoperative pain, no previous studies have evaluated the various doses of IM ketorolac for non-inferiority in the treatment of acute MSK pain. Of note, we chose a pain level of 20 mm on

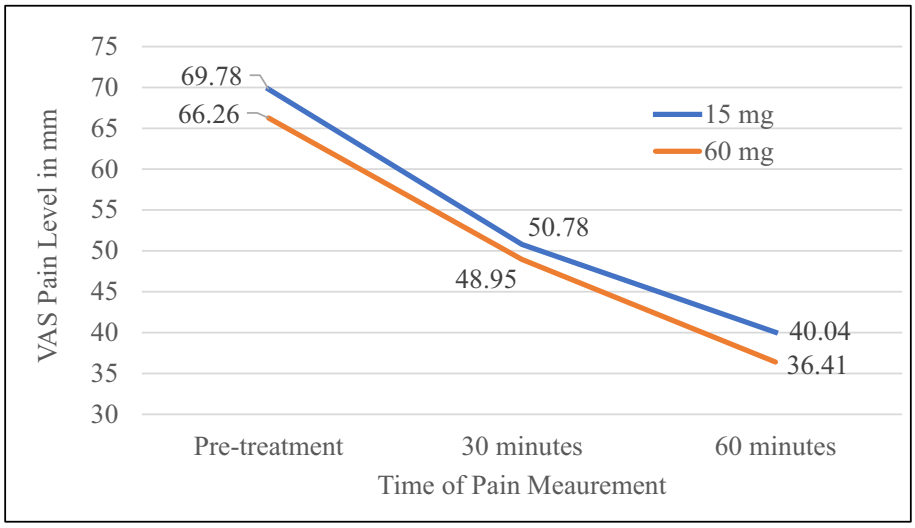

Fig. 1. Reduction in VAS pain (in millimeters) level after single IM injection of ketorolac at 15 mg and 60 mg.

Table 3
Dose-dependent comparisons of pain reduction at 30-min and 60-min after IM ketorolac administration.

Pain reduction	15 mg dose ($n = 55$)		60 mg dose ($n = 55$)		Mean difference	95% CI	p
	Mean	SD	Mean	SD			
At 30 min	−18.9	17.7	−17.3	18.3	−1.7	−8.49–5.14	0.63
At 60 min	−29.7	22.5	−29.9	23.1	0.1	−8.50–8.74	0.98

the VAS as an inclusion criterion to maximize recruitment of participants. The authors acknowledge that ketorolac does not have a labeled indication for mild pain. However, participation in the study was completely voluntary and with the knowledge that they would receive an IM injection of a NSAID to help decrease their pain. Furthermore, only 17 subjects (15% of total) that reported a VAS score of less than 50 mm.

The adverse effects reported in this study are concordant with previous literature demonstrating a dose dependence of adverse effects related to the administration of ketorolac. A significantly higher incidence of subjective adverse effects was detected in the 60 mg group than the 15 mg group. Our secondary outcome assessing for dose dependence of adverse effects was in-line with Garcia-Rodriguez et al. where they demonstrated a significant increase in relative risk for gastrointestinal bleeding with higher doses of IM and oral (PO) ketorolac [15]. Though their study evaluated relative risk of GI bleeds, rather than overall adverse effects, Strom et al. demonstrated a clear dose-dependence with higher doses of ketorolac, similar to ours [16]. Differing from previous literature, our study was the only one to assess for adverse effects at the time of administration of ketorolac. While none of the patients in the lower dose IM ketorolac group experienced any adverse effects, several in the higher dose group experienced burning at the IM injection site.

4.1. Limitations

This study has several important limitations. This study was conducted at a single ED in which all of the study participants were Department of Defense (DoD) or Veterans Affairs (VA) beneficiaries. Eighty-two percent of the sample were active-duty military whit the

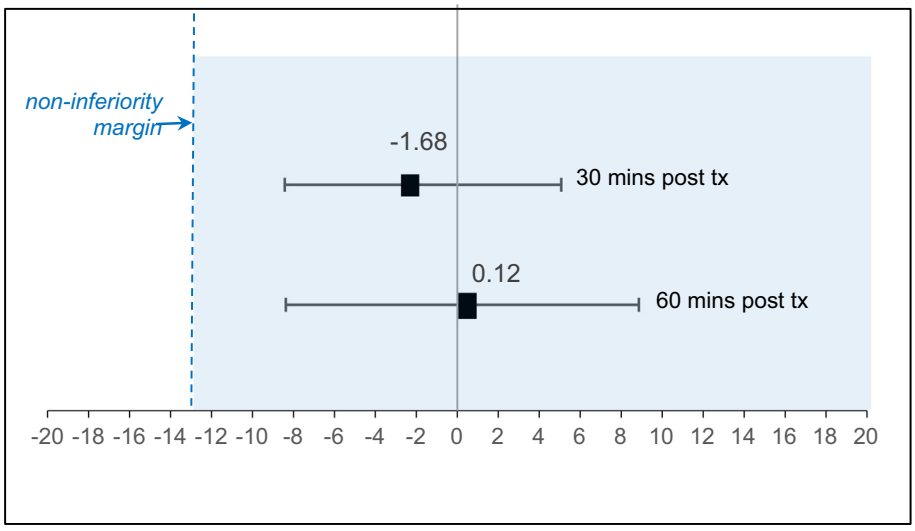

Fig. 2. Mean difference with 95% CI in VAS pain reduction between 15 mg and 60 mg groups at 30 and 60-min. The mean difference is represented by the solid black square with the horizontal bar being the 95% CI.

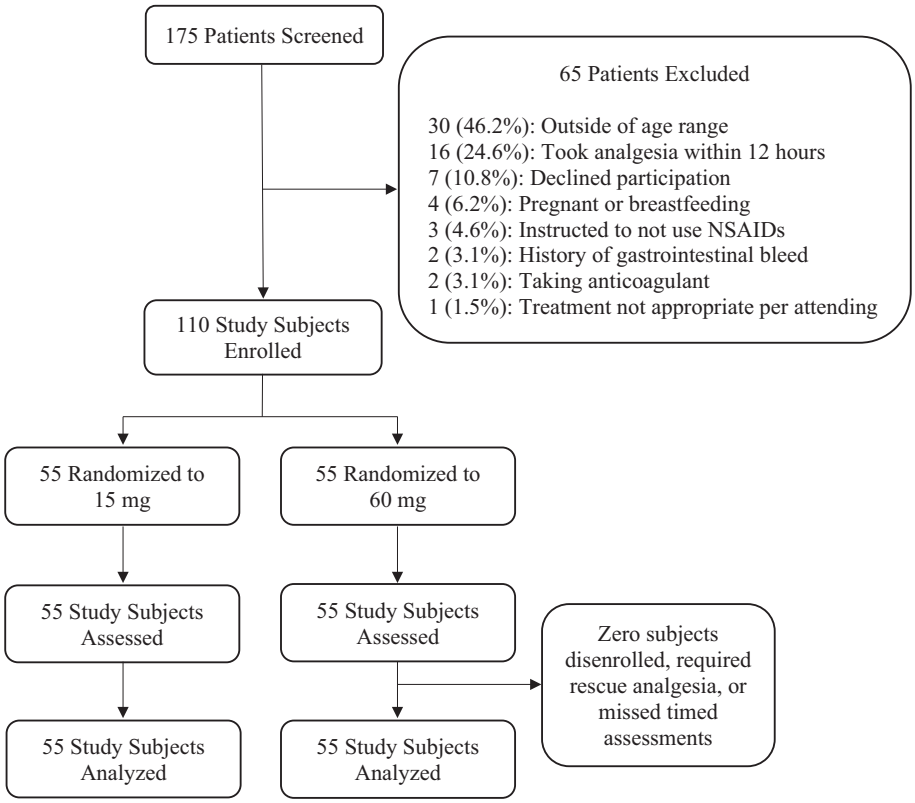

Fig. 3. Flow diagram for screened and enrolled study subjects.

remaining 28% either civilian or VA beneficiaries. While these patients represent a heterogeneous sampling of the U.S. population, portions of the population may not have been represented including uninsured patients, undocumented immigrants, illicit drug abusers, and the undomiciled population. Missing these groups may limit the generalizability of this study. Additionally, the exclusion criteria limited the group of enrolled study subjects. In developing the study design, patients triaged as ESI 1–3 were excluded as we believe they were more likely to require stronger therapies for pain control or may have had multi-organ dysfunction limiting the use of NSAIDs. This study did not evaluate the effectiveness of ketorolac in this patient cohort, potentially excluding extrapolation of our results to patients with higher acuity complaints or higher level of pain. Another limitation is that adverse effects in this study were only examined up to 60 min after the administration of ketorolac. Some of the well-known adverse effects of ketorolac include renal injury and gastrointestinal bleedings, which were not evaluated in this study.

Furthermore, there are several limitations inherent in the methodology of this study. As this study was designed as a non-inferiority trial, we were unable to establish superiority of the various doses of ketorolac in management of pain and were only able to observe whether a 15 mg dose of IM ketorolac is non-inferior to a 60 mg dose. While previous studies evaluating the efficacy of ketorolac used a numeric rating scale, and we utilized a VAS. Other studies commented that the VAS would take too long to use in the ED. In our experience conducting this study, this was not true. The study subjects were able to easily use the VAS after simple instructions, and we found it to be an efficient and effective tool for monitoring changes in patients' perceptions of pain.

While these limitations may impact the generalizability of our study, this study provides strong evidence that a 15 mg dose of IM ketorolac is non-inferior to a 60 mg dose of IM ketorolac for the treatment of acute MSK in adult patients presenting to the ED.

Table 4
Comparisons by pain location of pain reduction at 30-min and 60-min after ketorolac IM administration.

	Back/neck pain ($n = 37$)		Other pain locations ($n = 73$)		
Pain reduction	Mean	SD	Mean	SD	p
At 30 min	−12.46	14.96	−21.04	18.75	0.017
At 60 min	−22.38	20.54	−33.56	22.95	0.014

5. Conclusion

A 15 mg IM dose of ketorolac was found to be non-inferior to a 60 mg dose for short-term pain relief of acute MSK pain in adults presenting to an ED. Subjective adverse effects, while not numerous, were more often reported with the 60 mg dose. Discontinuing the practice of ordering 60 mg IM doses of ketorolac in place of a lower dose for acute MSK pain should be considered.

Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

Declaration of Competing Interest

None.

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