Low-Dose Short-Term Scheduled Ketorolac Reduces Opioid Use and Pain in Orthopaedic Polytrauma Patients: A Randomized Clinical Trial

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Objective: To determine whether scheduled low-dose, short-term ketorolac is associated with reduced length of stay, opioid use, and pain in orthopaedic polytrauma patients.

Design: Double-blinded, randomized controlled trial.

Setting: One Level 1 trauma center.

Patients: From August 2018 to October 2022, 70 orthopaedic polytrauma patients between 18 and 75 years of age with a New Injury Severity Score > 9 were randomized. Seventy participants were enrolled, with 35 randomized to the ketorolac group and 35 to the placebo group.

Intervention: The intervention used was 15 mg of intravenous (IV) ketorolac every 6 hours for up to 5 inpatient days or 2 mL of IV saline in a similar fashion.

Main Outcome Measurements: Length of stay (LOS), morphine milligram equivalents, visual analog scale, and complications.

Results: Study groups were not significantly different regarding age, body mass index, and New Injury Severity Score ($P > 0.05$). The median LOS was 8 days (interquartile range, 4.5–11.5) in the ketorolac group compared with 7 days (interquartile range, 3–10) in the placebo group ($P = 0.275$). Over the 5-day treatment period, the ketorolac group experienced a 32% reduction in average morphine milligram equivalents ($P = 0.013$) and a 12-point reduction in baseline-adjusted mean visual analog scale ($P = 0.037$) compared with the placebo group. There were no apparent short-term adverse effects in either group.

Conclusions: Scheduled low-dose, short-term IV ketorolac was associated with significantly reduced inpatient opioid use and pain in orthopaedic polytrauma patients, with no significant difference in LOS and no apparent short-term adverse effects. The results support the use of scheduled low-dose, short-term IV ketorolac for acute pain control among orthopaedic polytrauma patients. Further studies are needed to delineate lasting clinical effects and potential long-term effects, such as fracture healing.

Key Words: orthopaedic polytrauma, acute pain management, IV ketorolac, decreased opioid use, nonopioid pain management, morphine milligram equivalent, visual analog scale

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Acute pain after polytraumatic injury can be difficult to control. Traditionally, opioids served as the foundation for inpatient pain management, despite their failure to target the inflammatory response after musculoskeletal trauma and their potential for complications, including chronic use and dependency.[1–3] This is especially relevant in the treatment of polytrauma patients because these patients are at risk of developing various posttraumatic complications, including posttraumatic pain (PTP).[4–6] Inadequate acute pain control after polytrauma is associated with physical disability,

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delayed rehabilitation, and inability or delayed return to work.[4–6] Despite the potential for long-term negative sequela from poorly controlled acute pain, adequate analgesia among polytrauma patients is often inconsistent and insufficient.[7,8]

Recently, clinical practice has begun moving away from the use of opioid monotherapy for pain management after acute musculoskeletal injury. Multimodal analgesia (MMA) is a concept that incorporates the synergistic effect produced by targeting different pain pathways. MMA consists of a combination of standardized doses of opioids with other analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, skeletal muscle relaxants, both local and regional anesthesia, and psychotherapy. MMA is the current recommendation of the Orthopaedic Trauma Association Musculoskeletal Pain Task Force because it is associated with reductions in both short-term and long-term opioid use after orthopaedic trauma.[9–11] Despite a recent push for MMA, orthopaedic surgeons may be hesitant to use NSAIDs in fracture patients because of concern for bone healing. However, withholding NSAIDs may also cause harm by increasing narcotic requirements in patients. There remains a need for further study to further clarify the effect of NSAIDs on fracture healing.[12,13] Although some studies have shown opioids to be more efficacious analgesics compared with NSAIDs, adding NSAIDs to opioid treatment has been shown to reduce opioid requirements and opioid-related side effects.[10,14,15] Therefore, NSAIDs may serve as a promising adjuvant for obtaining perioperative and postoperative musculoskeletal pain control.

Ketorolac has been approved as an injectable NSAID analgesic since 1989.[16] Multiple studies have shown that ketorolac is statistically superior in pain intensity reduction, does not alter hemodynamics, and poses a better safety profile compared with morphine.[17–21] Compared with other NSAIDs, ketorolac is one of the most commonly used intravenous (IV) NSAIDs in the hospital setting for treating acute pain and may result in better moderate-to-severe pain relief and less stomach irritation.[22–24] In addition, ketorolac has been shown to provide effective acute pain relief in patients with moderate-to-severe pain, as well as both perioperative and postoperative analgesia after single-limb musculoskeletal injury.[15,23,25] Although ketorolac has been shown to be effective after musculoskeletal injury, there are no randomized controlled trials (RCTs) to date demonstrating its efficacy in treating orthopaedic polytrauma patients. Therefore, the objective of this study was to investigate the efficacy of ketorolac in treating acute and postoperative pain after polytrauma. This study was designed as a double-blinded RCT to determine whether the administration of a scheduled low-dose, short-term NSAID, ketorolac, in combination with standard-of-care (SOC) MMA, is associated with decreased length of stay (LOS), acute pain, and opioid intake in orthopaedic polytrauma patients. The authors chose a low-dose regimen of IV ketorolac with a treatment period of 5 inpatient days per Food & Drug Administration recommendation.[26]

MATERIALS AND METHODS

After obtaining institutional review board approval at a single Level I trauma center and clinical trial registration (ClinicalTrials.gov; NCT03671746), potential subjects were screened, recruited, and enrolled from August 2018 to October 2022.

Patient Population

Patients 18–75 years of age with a New Injury Severity Score (NISS) greater than 9, who had sustained a musculoskeletal injury requiring surgical treatment were included. Patients outside of this age range, with an injury that had occurred more than 24 hours before presentation, with a pre-existing inflammatory condition (eg, inflammatory arthropathy or inflammatory bowel disease), or with pre-existing comorbidities (eg, myocardial infarction; coronary artery disease; chronic heart, liver, or renal failure; chronic obstructive pulmonary disease; emphysema; asthma; or AIDS) were excluded. Patients who had contraindications to receiving NSAID therapy, such as patients in hemorrhagic shock, at risk of hemorrhage, with active gastrointestinal bleeding or ulceration, NSAID allergy, or coagulopathy, were excluded. Finally, patients who were pregnant, had sustained thermal injury, or with a history of chronic steroid and/or opioid use were also excluded.

In total, 70 participants with a median age of 36.8 years (interquartile range, 25.5–51.8) were enrolled, with 35 subjects randomized to the ketorolac group and 35 to the placebo group.

New Injury Severity Score Calculation

After physical examination and radiographic assessment of the subject's injuries, a single fellowship-trained orthopaedic trauma surgeon calculated the NISS score of each subject. NISS is based on an anatomical scoring system that provides an aggregate score for patients with multiple traumatic injuries. Each injury is assigned an Abbreviated Injury Severity score, allocated to one of the following 6 body regions: face, head and neck, chest, abdomen, extremities (including pelvis), and external. The sum of the squares of the top 3 Abbreviated Injury Severity scores was calculated irrespective of body region. A NISS greater than 9 is defined as a moderate injury and was chosen as the minimum score required for study enrollment.[27,28] NISS values were confirmed by the institution's trauma registry.

Study Design

This was a single-center, randomized, double-blinded, two-arm, placebo-controlled study. The institution's Investigational Drug Service performed computer-generated randomization of the subjects in a 1:1 allocation ratio. The subjects, research personnel, and subject's treatment team were all blinded to the subject's group assignment. The ketorolac group received 15 mg of IV ketorolac every 6 hours for the first 5 inpatient days while the placebo group received 1–2 mL of IV normal saline in a similar fashion. Both regimens were started preoperatively and continued through inpatient day 5 or until discharge for subjects who had a LOS less than 5 days. The subjects' primary treatment teams during their hospitalization were instructed not to provide any additional NSAIDs during the 5-day treatment period. Subjects in both groups could receive additional SOC analgesics

according to hospital MMA protocol, which is summarized in Table 1. All subjects were given only Lovenox 30 mg subcutaneous twice daily for deep venous thrombosis prophylaxis per hospital protocol (see **Table, Supplemental Digital Content 1**, http://links.lww.com/JOT/C93).

Outcomes

The primary outcome was inpatient LOS measured in days. Secondary outcomes of interest included opioid consumption measured using morphine milligram equivalent (MME) and pain intensity measured using visual analog scale (VAS) collected from enrollment to inpatient day 5. MMEs were calculated daily by research personnel during the 5-day treatment period according to each subject's Medication Administration Record. The investigators used MME as a standardized method to compare opioid use between the ketorolac and placebo groups. Conversion factors used were provided by the Centers for Disease Control and Prevention.[29] VAS is an instrument that attempts to capture the perception of pain, which is often considered a continuum that is not easily measured in discrete values or categories.[30] Daily VAS pain scores were obtained by research personnel at enrollment and at subsequent 24-hour intervals during the 5-day treatment period. Subjects were also monitored daily for complications and adverse events, such as acute renal failure, excessive hemorrhage, gastric ulceration, or allergic reaction.

Statistical Analysis

Pretrial sample size calculations were performed regarding LOS because this was the primary outcome measure of the clinical trial. Using a significance level of 0.05 and an assumed SD of 1.5 days, a sample size of 42 patients per group (84 total) would yield 80% power to detect a difference of 0.928 days in average LOS between the placebo and ketorolac groups. Because the trial was conducted in the mid of a global pandemic, we were only able to obtain a sample size of 35 patients per group. Allowing for a dropout rate up to 25%, recruitment was originally planned for 56 patients per group. Power calculations were performed using nQuery 8.5 (Statistical Solutions Ltd; Cork, Ireland).

Group-level summary statistics were calculated for clinical and demographic variables, and differences between the 2 groups were evaluated using two-sample *t* tests for quantitative measures and Fisher exact tests for categorical measures, as appropriate. Owing to right skewness, LOS and MME values were log-transformed before analysis and summarized using medians and interquartile ranges for each group. Group-level VAS pain scores were summarized using means and standard deviations. An analysis of variance model was fit to compare log-transformed LOS between the 2 groups. Linear mixed models were used to estimate differences in VAS pain scores and log-transformed MME values over time between the 2 groups. The VAS model was adjusted for baseline levels as a covariate, which differed significantly between groups. Likelihood ratio testing and Akaike information criterion were used to select appropriate covariance structures in each case. A Kenward–Roger adjustment was used to correct for negative bias in the standard errors and degrees of freedom calculations. Throughout the study, a P value of less than 0.05 was considered significant. All analyses were completed in SAS 9.4 (SAS Institute Inc.; Cary, NC).

TABLE 1. MMA Protocol

Scheduled
Acetaminophen* 1000 mg tablet PO q6h for pain
Gabapentin 100 mg capsule PO, 3 TID × 7 d then 1 TID
Ketorolac* 15 mg IV q6h (stopped after 4 doses)
As needed medication (PRN)
Oxycodone Taper
POD#0–1, 5–10 mg q4h
POD#2, 5 mg q4h
POD#3–5, 5 mg q6h
POD#6–7, 5 mg q8h
Ibuprofen* 400 mg tablet, 1 PO q6h PRN for pain (begins on POD #1 after 4 doses of ketorolac)
Methocarbamol 750 mg tablet, 1 q6h PRN for muscle spasms
Morphine IV 2–4 mg q 2h PRN for severe pain
Tramadol 50 mg tablet PO, q4h PRN for pain unresponsive to nonopioids

*NSAID, temporarily held during the 5-day treatment period.

RESULTS

Study groups were not significantly different regarding age, body mass index, NISS, and total number of surgeries ($P > 0.05$) (Table 2). Group-level summary statistics for LOS, MME, and VAS are presented in Tables 3–5, respectively. Over the 5-day treatment period, the ketorolac group experienced a 32% reduction in average opioid intake ($P = 0.013$) and a 12-point reduction in baseline-adjusted mean VAS ($P = 0.037$) compared with the placebo group. Hospital LOS was not significantly different between the 2 groups ($P = 0.275$). There was a notable decrease of 21 admitted subjects past inpatient day 3, with only 49 subjects remaining hospitalized on Day 4 and day 43 remaining on Day 5. However, both groups were evenly distributed regarding the number of patients with less than 5 days of admission ($P > 0.05$) (Tables 4 and 5). When aggregated from enrollment to inpatient Day 3, the baseline-adjusted mean VAS was an estimated 8.8 points lower in the ketorolac group compared with the placebo group ($P = 0.156$). In addition, the ketorolac group still experienced a 27.9% reduction in mean MME compared with the placebo group ($P = 0.036$) when aggregated from enrollment to inpatient Day 3. LOS comparisons by group are illustrated in **Supplemental Digital Content 2** (see **Figure**, http://links.lww.com/JOT/C94) while MME and VAS comparisons by group and inpatient day are illustrated in **Supplemental Digital Content 3 and 4** (see **Figures**, http://links.lww.com/JOT/C95, http://links.lww.com/JOT/C96), respectively. No complications or adverse events occurred throughout this study, such as acute renal failure, excessive hemorrhage, gastric ulceration, or allergic reaction.

DISCUSSION

This double-blinded RCT demonstrated that a 5-day course of scheduled IV ketorolac did not decrease LOS but

TABLE 2. Patient Characteristics

Demographic Variable	Sublevel	Ketorolac (n = 35)	Placebo (n = 35)
Age (y)		39.5 ± 17.2	40.0 ± 16.2
BMI		28.2 ± 7.3	29.5 ± 6.4
NISS		14.0 ± 5.2	15.1 ± 6.4
Surgery count		1.2 ± 0.6	1.4 ± 0.7
Surgery count	1	30 (85.7%)	24 (68.6%)
	2	4 (11.4%)	8 (22.9%)
	3	—	3 (8.6%)
	4	1 (2.9%)	—

BMI, body mass index.

did decrease acute pain and inpatient opioid intake among orthopaedic polytrauma patients. The ketorolac group experienced a significant decrease in MME from enrollment to inpatient Days 3 and 5 and a significant decrease in baseline-adjusted VAS from enrollment to inpatient Day 5. To the best of the authors' knowledge, this is the first RCT to study the efficacy of scheduled IV ketorolac use in orthopaedic polytrauma patients, whereas previous studies have primarily focused on single extremity injury. For example, McDonald et al demonstrated that perioperative ketorolac decreased opioid consumption and median VAS scores in the early postoperative period after ankle fracture surgery.[15] Kinsella et al[25] demonstrated that postoperative ketorolac improved overall analgesia in minor orthopaedic surgery and reduced supplemental opioid use in major orthopaedic surgery, where major surgery was defined as any procedure that fulfilled at least 2 of the following criteria: blood loss greater than 100 mL and analgesic requirement in the first 24 hours of morphine 10 mg every 4 hours or requirement of IV fluid administration in the first 24 hours

Regarding IV NSAIDs use in orthopaedic patients, Weisz et al[31] demonstrated that scheduled administration of IV ibuprofen within 48 hours after injury provided adequate analgesia, prolonged time to first narcotic administration, and reduced opioid use in orthopaedic trauma patients. Our study reaffirms these findings and supports that longer duration IV ketorolac is safe and efficacious for a prolonged period of inpatient admission of 5 days. Administration of IV ibuprofen preoperatively and postoperatively has also been shown to significantly reduce pain and morphine consumption in patients who underwent elective, single-site orthopaedic or abdominal surgery.[32,33] Finally, Zhou et al[34] has recently shown that intermittent administration of IV ibuprofen within 24 hours postoperatively

TABLE 3. Group-Level Summary Statistics of Length of Stay*

Group	Median (IQR†)	*P*‡
Ketorolac (n = 35)	8 (4.5–11.5)	0.275
Placebo (n = 35)	7 (3–10)	

*Length of stay measured in days.
†IQR, interquartile range (first quartile–third quartile value).
‡*P*-value comes from analysis of variance model on log-transformed values of length of stay, correcting for heavy right skewness.

TABLE 4. Group-Level Summary Statistics of MME

Group	Day	*n*	Median	IQR*
Ketorolac	0 (enrollment)	34	86	38–120
	1	34	48.75	19–82
	2	31	53	26–75
	3	28	38.25	28–75
	4	25	30	23–60
	5	23	30	18–52
Placebo	0 (enrollment)	35	82.5	49–118
	1	34	67.75	48–81
	2	29	62	38–90
	3	26	72	45–99
	4	24	60	28–78
	5	20	63.75	32–88

*IQR, interquartile range (first quartile–third quartile value).

significantly decreased morphine use and VAS pain scores in patients undergoing orthopaedic or abdominal surgery.

We hypothesized that scheduled ketorolac administration would result in improved pain control and thus lead to decreased LOS. Multiple orthopaedic studies have shown that pain control has an impact on hospital LOS.[35–38] Although we did not see this effect in this RCT, the results of this study support implementation of low-dose, short-term IV ketorolac therapy as part of the MMA pathway. This is in sharp contrast to strong reliance on opioids, which historically have been first-line treatment for acute pain management of musculoskeletal injuries. However, increased inpatient opioid use among orthopaedic patients is associated with greater pain, less satisfaction with pain control, and continued chronic opioid use.[10,39–42] Given the significant variability that exists in opiate-prescribing practices after orthopaedic injury, the lack of universal opiate-prescribing recommendations, and the rising rates of opioid-related deaths as seen in the current opioid epidemic,[43,44] changes in pain management after musculoskeletal injury are necessary, especially in polytrauma patients who may be at increased risk of developing

TABLE 5. Group-Level Summary Statistics of VAS Pain Scores

Group	Day	*n*	Mean	SD
Ketorolac	0 (enrollment)	33	68.2	24.4
	1	31	42.7	25.6
	2	28	47.4	27.7
	3	25	56.3	26.0
	4	23	43.3	24.0
	5	17	52.6	21.9
Placebo	0 (enrollment)	35	55.1	27.5
	1	32	52.2	31.3
	2	25	53.9	26.5
	3	24	54.1	27.3
	4	20	59.5	26.9
	5	16	59.2	25.6

SD, standard deviation.

chronic pain and opioid use.[45,46] The lower extremity assessment project study showed that inadequate pain control in the early recovery period after high-energy lower extremity trauma was the largest predictor of long-term chronic pain 7 years postinjury.[45] In addition, Normal et al showed that a one-half SD increase in inpatient pain intensity was associated with a seven-fold increase in posttraumatic stress disorder.[47] Although the etiology of chronic pain may be multifactorial, a Swedish study of 13,309 injured patients and 70,621 control patients found musculoskeletal injury to be the strongest risk factor for chronic opioid use in opioid-naive patients.[46]

Orthopaedic trauma patients commonly develop PTP after injury.[48] Because the SOC for PTP still relies partially on opioid management, these patients continue to have an increased risk for chronic opioid use and dependency.[1,49,50] NSAIDs offer a promising analgesic for managing acute and perioperative pain, where perioperative NSAIDs use has been shown to decrease pain and short-term opioid use after surgery.[14,15,19,24,25,34,51]

The presented study provides insight into the effect of a scheduled low-dose, short-term IV NSAID regimen on opioid use and pain over a 5-day treatment period in orthopaedic polytrauma patients. Although it has been shown that scheduled IV NSAID use during the first 2 inpatient days after orthopaedic trauma can be opioid-sparing and provide adequate analgesia,[31] our group was able to demonstrate that this can be achieved further in orthopaedic polytrauma patients during the first 5 inpatient days. These findings have the potential to alter the SOC for orthopaedic polytrauma acute pain management, serving as evidence that IV ketorolac may be administered safely in a scheduled fashion to patients who have sustained moderate-to-severe musculoskeletal injuries.

The authors acknowledge several limitations to this study. First, we were not able to reach our originally planned sample size of 56 patients per group. We attribute this limitation to the challenges that came with recruiting patients in the mid of the COVID-19 pandemic because our institution suspended all clinical trial enrollment for several months. Second, owing to a transition in our institution's electronic medical record that took place in 2021, we are unable to provide exact numbers of how many patients were excluded and for what reasons. Third, although research personnel recruited subjects who had an anticipated hospital LOS of at least 5 days, not all subjects were hospitalized for this length of time. There was a notable decrease in the number of subjects admitted past inpatient Day 3. Nonetheless, both groups were evenly distributed regarding patients with less than 5 days of admission. When analyzed from enrollment to inpatient Day 3, we found a significant decrease in MME and a notable decrease in VAS in the ketorolac group compared with the placebo group. We acknowledge that VAS scores collected at 24-hour intervals from the time of enrollment may also serve as a limitation because VAS can fluctuate depending on the timing of pain medication administration. However, with patients still receiving as-needed SOC MMA and the study team being blinded to ketorolac or placebo administration, we believed obtaining VAS scores at 24-hour intervals from the time of enrollment maintained uniformity between groups. Furthermore, the patients' primary treatment teams were responsible for providing as-needed pain medication, and it was at their discretion as to the amount of analgesia patients received. Although the authors acknowledge this subjectivity may be concerning, we contend that the same MMA protocol was used for patients in both groups by their primary treatment team who was blinded to the patient's group assignment. As study groups were balanced regarding NISS and surgery count, we believe the double-blinded, randomized design of this study mitigates concern for potential bias in pain medication administration between the 2 groups.

Owing to the volatile nature of polytrauma, there is likely variability in the type and severity of injuries sustained irrespective of NISS score, number of surgeries and procedures, and time between surgeries. However, this only makes the results more generalizable to the heterogenous nature of polytrauma patients. Additional bedside procedures that were not captured in this study, such as thoracostomy placement, closed reduction, skeletal traction, laceration repair, endotracheal intubation, or central line placement, may also have served as factors that contributed to subjects' pain and opioid intake. However, owing to RCT design of this study, one would expect both groups to have uniform distributions of such additional procedures. In addition, we recognize that the selected study criteria excluded many patients who presented with polytrauma, as patients with comorbidities or who had significant risk for hemorrhage were excluded. However, that is an inherent limitation of scheduled NSAID administration, as such therapy is contraindicated in patients at risk for hemorrhage, renal compromise, and/or history of gastric ulcers. Finally, this study did not assess fracture healing and nonunion, which has been a point of contention in implementing comprehensive NSAID use in fracture patients due to concerns with bone healing. A recent systematic review by Marquez et al highlighted the need for higher-quality data using prospective RCTs, such as the Pain Study,[12] to determine the effect of NSAIDs on bone healing.[13] The presented study would have been underpowered to detect a meaningful association between bone healing and NSAID use.

CONCLUSION

Scheduled use of low-dose, short-term IV ketorolac was not associated with decreased LOS but was associated with significantly reduced inpatient opioid use and acute pain in orthopaedic polytrauma patients with no apparent short-term adverse effects. The results support the use of scheduled low-dose, short-term IV ketorolac for acute and perioperative pain control in noncontraindicated orthopaedic polytrauma patients. Future research with a larger sample is needed to delineate lasting clinical effects and potential long-term effects, such as psychosocial factors that also contribute to pain, in addition to fracture healing.

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