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OTA HIGHLIGHT PAPER

Intravenous Ibuprofen Reduces Opioid Consumption During the Initial 48 Hours After Injury in Orthopedic Trauma Patients

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Objectives: To evaluate the efficacy of intravenous (IV) ibuprofen (Caldolor) administration in the management of acute pain in orthopedic trauma patients and to minimize opioid use.

Design: Randomized controlled trial, double-blind, parallel, placebo-controlled.

Setting: Level 1 Trauma Center.

Patients: A total of 99 consecutive orthopedic trauma patients with fractures of the ribs, face, extremities, and/or pelvis were randomized to receive either 800 mg IV ibuprofen (53 patients) or placebo (44 patients) administered every 6 hours for a total of 8 doses within 48 hours of admission and the same PRN medications along with 20-mg IV/PO Pepcid twice a day. To establish pain reduction efficacy, the analysis was consequently performed in the modified intent-to-treat group that included 74 randomized subjects with a baseline pain score greater than 2. The primary outcomes were reduction in opioid consumption and decrease in pain intensity (PI).

Intervention: Administration of study medications.

Outcome Measurements: PI measured by Numerical Rating Scale, opioid consumption adjusted to morphine equivalent dose, and time to first narcotic administration.

Results: The 2 groups had comparable baseline characteristics: age, sex distribution, mechanism of injury, type of injury, injury severity score, and PI. IV ibuprofen statistically significantly reduced opioid consumption compared with placebo during the initial 48-hour period ($P = 0.017$). PI calculated as PI differences was statistically different only at 8-hour interval after Caldolor administration. Time to first narcotic medication was significantly longer in the Caldolor group (hazard ratio: 1.640; 95% confidence interval, 1.009–2.665; $P = 0.046$).

Conclusions: IV ibuprofen provided adequate analgesia, prolonged time to first narcotic administration, and was opioid-sparing for the treatment of pain in orthopedic trauma patients, which makes Caldolor a recommended candidate for managing acute pain in the diverse orthopaedic trauma population.

Key Words: orthopaedic trauma, acute pain management, IV ibuprofen, opioid consumption, Caldolor, decreased narcotic requirements, pain intensity difference

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

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INTRODUCTION

Opioid use can put patients' health at risk, and current overdose rates have reached epidemic levels. Even when opioid use involves a prescription, it can be dangerous. Of the 47,600 opioid overdose deaths in the United States in 2017, 17,029 (35.8%) were due to prescription opioids.[1]

Although representing only 2% of all physicians in the United States, orthopaedic surgeons are the fourth main prescribers of opioids (7.7% of total opioid prescriptions) after primary care physicians, internists, and dentists.[2,3] As Ruder et al[4] reported in a recently published study, pain management after orthopaedic trauma continues to be opioid-centric despite a population at risk, and that a move away from opioid monotherapy is needed.

Clinical practice guidelines for pain management in acute musculoskeletal injury approved by the Orthopaedic Trauma Association recommend the use of multimodal analgesia (MMA) as opposed to opioid monotherapy for pain control; however, it was also emphasized that there is a paucity of literature in the orthopaedic trauma population.[5]

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The results of this study were presented as a podium presentation at the 35th Annual Orthopaedic Trauma Association meeting, September 25–28, 2019, Denver, CO.

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Adjunctive agents for pain relief in MMA may include nonsteroidal anti-inflammatory agents (NSAIDs).

Intravenous (IV) ibuprofen (Caldolor, Cumberland Pharmaceuticals, Nashville, TN) was approved by the Food and Drug Administration for use in the United States and is indicated for management of mild to moderate pain as a single therapy and for management of moderate to severe pain as an adjunct to opioid analgesics.[6] Similar to oral ibuprofen, the IV formulation can inhibit both COX-1 and COX-2.

The goal of our study was to evaluate the efficacy of IV ibuprofen (Caldolor) administration in the management of acute pain in orthopedic trauma patients and to minimize opioid use.

PATIENTS AND METHODS

This institutional review board approved prospective study was conducted at a state-certified Level 1 Trauma Center. The study was approved by the Western Institutional Review Board (WIRB # 20121749) and registered at the clinical trial registry (clinicaltrials.gov; NCT02152163).

Patients

Eligible patients were trauma patients between the ages of 18 and 75 years with adequate IV access who were able to self-report and communicate pain severity and who were consecutively admitted to the trauma intensive care unit (ICU) or trauma step-down units with a fracture of the ribs, face, extremities, and/or pelvis. Any patients with history of ulcers, gastritis, previous gastrointestinal bleeding, bleeding disorders, allergy, or hypersensitivity to any component of IV ibuprofen, aspirin, NSAIDs, or Cox-2 inhibitors were not eligible for the study. Any patient with renal impairment, intracranial, or spinal cord trauma, or recent history of intracranial surgery or stroke was also not eligible for the study. Patients who were pregnant or breastfeeding were excluded from the investigation.

Study Design

This was a single-center, randomized, double-blind, parallel-group, placebo-controlled study. Eligible patients who signed the informed consent were randomized to either IV Ibuprofen (Caldolor) or Placebo through a computer-generated randomization list maintained at the pharmacy with an allocation ratio of 1:1. With the exception of the pharmacy, all other staff, including the principal investigator, study coordinator, and trauma nurses and the patients were blinded as to the treatment they received. To maintain the double-blind protocol, all IV bags had identical appearance and label. Patients received a total of 8 doses of either the medication (800 mg IV ibuprofen) or the placebo over 30 minutes, every 6 hours, along with 20-mg IV/PO Pepcid for 48 hours. Patients had pain measured using a Numerical Rating Scale that ranged from 0 (no pain) to 10 (worst possible pain).[7] A baseline pain intensity (PI) score was obtained before medication administration. Additional pain medication was provided on as-needed (PRN) basis per standardized order set. Pain was assessed before and after administration of any pain medication. For purposes of the study, pain assessments were obtained for both treatment groups from nurse charting at hours 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 and then twice daily for a total of 5 days. The focus on the first 48 hours was based on previous data that patients with fractures experienced the worst pain in the first 48 hours after injury.[8] Patients received the same PRN pain medications and IV Pepcid dosage whether they were in the placebo or the IV ibuprofen group. The administration of PRN pain medications was based on the patient's self-assessment of pain using the Numerical Rating Scale. The protocol defined standardized PRN pain regimen for both groups was

1. Minimal pain (rated as a 1–2)
   a. Tylenol 650 mg PO/PRN Q4h
2. Minimal—moderate pain (rated as a 3–4)
   a. Oxycodone 5 mg 1 tab PO q4Q4h
3. Moderate pain (rated as a 5–6)
   a. Oxycodone 10 mg PO q4Q4h
   b. Morphine 1 mg IV Q4h
4. Moderate–severe pain (rated as a 7–8)
   a. Morphine Sulfate 2 mg IV Q3h
   b. Dilaudid 1 mg IV Q4h
   c. May give 1 tab of Oxycodone 5 mg PO Q4h for breakthrough pain
5. Severe pain (rated as a 9–10)
   a. Morphine sulfate 4 mg IV Q3
   b. Dilaudid 2 mg IV Q3
   c. May give 1 tab of Oxycodone 5 mg PO Q4h for breakthrough pain

After the 48-hour period, Caldolor 400–800 mg could be given every 6 hours PRN for pain at the discretion of the treating physician.

Efficacy Evaluation

The primary efficacy endpoint was the amount of opioid medication taken during the initial 48 hours. All opioid medication taken was converted to an oral morphine equivalent dose in mg before conducting the analysis. The secondary efficacy endpoints included PI difference (PID) during the initial 48-hour period and over the 5-day period, length of hospital stay, and rate of treatment failure. PID was defined as baseline PI score minus postbaseline PI score. For the PI scores, analysis windows were defined as 4-hour time ranges with the target collection time point as the midpoint of the window (ie, ± 2 hours before and after the scheduled time). The PI scores used in the analysis were the average of all pain scores recorded within the analyzed window. The baseline PI score was defined as the last PI value before administration of the study drug. All efficacy analyses were conducted using the modified intent-to-treat (mITT) population defined as randomized patients with a baseline pain score greater than 2. Since the objective of the study was to determine if IV ibuprofen can decrease pain in orthopedic trauma patients and decrease the use of opioid analgesics, we only included subjects with at least moderate pain (ie, baseline pain greater than 2) in the mITT population, which resulted in 74 subjects in this group (Placebo—35 patients, and Caldolor—39 patients).

Treatment failure was defined as the requirement of additional pain medications within the 48-hour window after initiation of study treatment. As an additional objective assessment of the rate of treatment failure, the time to first narcotic medication was calculated as the time in hours from the initiation of study drug to the first time that a narcotic medication was administered. Patients who did not receive a narcotic in the first 48 hours were censored at either 48 hours or the time of hospital discharge, whichever time was earlier.

Statistical Analysis

The primary efficacy endpoint regarding the amount of opioid medication was analyzed using the difference in least-square mean values (LS Means) from an analysis of covariance model with a fixed effect for treatment and baseline PI as a covariate. PID was analyzed using the same analysis of covariance model. The secondary efficacy endpoints of length of hospital stay and time to first narcotic medication were analyzed using the Kaplan–Meier estimation method. A Cox proportional hazards regression analysis with effects for treatment and baseline PI was performed to determine the hazard ratio (HR), the corresponding 95% confidence interval (CI), and to compare the treatment groups.

For the comparison of baseline tobacco, alcohol, recreational drugs, and pain medication usage between groups, χ^2 analysis was used with $P < 0.05$ considered as statistically significantly different.

Treatment assignment (Placebo or Caldolor) remained blind to all authors, until all results were obtained, and all statistical analysis had been completed.

RESULTS

A total of 99 patients were randomized and received study treatment. Efficacy analyses were performed on the mITT population of 74 patients. The demographic and baseline characteristics were comparable between the treatment groups and are represented for all randomized patients in Table 1 and for the mITT population in Table 2. For all randomized patients, the overall mean age was 42 years (range 19–76 years) and 74% were male. For the mITT population, the overall mean age was 42 years (range 19–76 years) and 78% were male. Most of the injuries were caused by motor vehicle collision (MVC) (72%) and were in the extremities (55%). The mean injury severity score was 12 for the mITT population and 11 for all patients. Baseline tobacco (23.9% vs. 26.4%, $P = 0.78$), alcohol (19.6% vs. 18.9%, $P = 0.93$), recreational drugs (17.4% vs. 7.5%, $P = 0.13$), and pain medication (0.1% vs. 1.9%, $P = 0.35$) usage among all 99 patients was not statistically different between the Caldolor and Placebo groups. In the mITT population, baseline tobacco (22.9% vs. 20.5%, $P = 0.81$), alcohol (20.0% vs. 17.9%, $P = 0.82$), recreational drugs (17.1% vs. 7.7%, $P = 0.21$), and pain medication (0% vs. 2.6%, $P = 0.34$) usage were also not statistically different between the Caldolor and Placebo groups. Types of injury distribution

TABLE 1. Demographics and Baseline Characteristics, All Randomized Patients

Variables	Placebo (n = 44)	Caldolor (n = 53)	*P*
Age (y) (mean; SD)	41.3 (15.8)	41.9 (16.3)	0.864
Gender (male) (%)	77.3% (34)	71.7% (38)	0.724
Injury (diagnosis)			NA
Ribs	31.8% (14)	41.5% (22)	
Face	15.9% (7)	22.6% (12)	
Extremities	63.6% (28)	58.5% (31)	
Pelvis	20.5% (9)	18.9% (10)	
Mechanism of injury			0.532
Fall	18.2% (8)	22.6% (12)	
MVC	79.5% (35)	66.0% (35)	
GSW	0.0%	1.9% (1)	
Penetration	0.0%	1.9% (1)	
Other	2.3% (1)	5.7% (3)	
ISS (mean; SD)	11 (6.4)	12 (5.7)	0.911
RTS (mean; SD)	7.8 (0.14)	7.7 (0.68)	0.217
Initial pain score (before first SDI) (mean; SD)	6 (3.0)	5 (3.3)	0.591
Initial pain score (before first SDI) category			0.451
No pain (0)	9.1% (4)	13.2% (7)	
Minimal pain (1–2)	2.3% (1)	11.3% (6)	
Minimal–moderate pain (3–4)	20.5% (9)	11.3% (6)	
Moderate pain (5–6)	13.6% (6)	18.9% (10)	
Moderate–severe pain (7–8)	27.3% (12)	26.4% (14)	
Severe pain (9–10)	18.2% (8)	17.0% (9)	

MVC, motor vehicle collision; GSW, gunshot wound; ISS, injury severity score; RTS, revised trauma score; SDI, study drug injection.

TABLE 2. Demographics and Baseline Characteristics, mITT Population

Variables	Placebo (n = 35)	Caldolor (n = 39)	*P*
Age (y) (mean; SD)	41.5 (16.0)	41.9 (17.4)	0.904
Gender (male) (%)	80.0% (28)	76.9% (30)	0.567
Injury (diagnosis)			NA
Ribs	31.4% (11)	48.7% (19)	
Face	17.1% (6)	20.5% (8)	
Extremities	57.1% (20)	53.8% (21)	
Pelvis	20.0% (7)	20.5% (8)	
Mechanism of injury			0.664
Fall	20.0% (7)	23.1% (9)	
MVC	77.1% (27)	66.7% (26)	
GSW	0.0%	2.6% (1)	
Penetration	0.0%	2.6% (1)	
Other	2.9% (1)	5.1% (2)	
ISS (mean; SD)	12 (7.0)	12 (5.6)	0.949
RTS (mean; SD)	7.8 (0.15)	7.7 (0.65)	0.345
Initial pain score (before first SDI) (mean; SD)	7 (2.3)	7 (2.1)	0.470
Initial pain score (before first SDI) category			0.659
No pain (0)	0.0%	0.0%	
Minimal pain (1–2)	0.0%	0.0%	
Minimal–moderate pain (3–4)	25.7% (9)	15.4% (6)	
Moderate pain (5–6)	17.1% (6)	25.6% (10)	
Moderate–severe pain (7–8)	34.3% (12)	35.9% (14)	
Severe pain (9–10)	22.9% (8)	23.1% (9)	

MVC, motor vehicle collision; GSW, gunshot wound; ISS, injury severity score; RTS, revised trauma score; SDI, study drug injection.

were also comparable between groups (% of fractured ribs, etc.) and went through similar treatment approaches by the same physician. The mean baseline pain score was 7 (range 3–10) with the patients fairly evenly distributed across the categories with the most patients (35%) having moderate–severe pain (pain score 7–8). Similar distributions of pain scores were observed in both treatment groups. The above presented comparison between all randomized patients, including m ITT population demonstrates that subjects were similar in their characteristics.

The amount of morphine equivalent given was significantly less in the Caldolor group as compared to the placebo group (difference in LS Means = −22.9 mg; 95% CI for difference, −41.4 to −4.2; *P*-value = 0.017; Table 3 and Fig. 1). The difference in observed mean values between the groups was −20.8 mg (95% CI, −39.8 to −1.8). The time course of mean PID over the entire 48 hours after start of infusion period showed better pain reduction in the Caldolor group as compared to the placebo group with significant reduction occurring at 8 hours after start of infusion (difference in LS Means = 1.1; 95% CI for difference, 0.2–2.0; *P*-value = 0.013; see **Supplemental Digital Contents 1 and 2**, http://links.lww.com/JOT/A976 and http://links.lww.com/JOT/A977). The difference in observed mean values between the groups was 1.4 (95% CI, 0.3–2.6). Most of the patients required at least one dose of pain medication during the 48 hours after the initiation of study treatment. There was only one mITT patient who did not require pain medication, and he was a Caldolor patient. The time to first narcotic was longer in the Caldolor group as compared to the placebo group (HR: 1.640; 95% CI, 1.009–2.665; *P*-value = 0.046; Table 3 and Fig. 2). The time to discharge was similar between the treatment groups (HR: 0.914; 95% CI, 0.559–1.495; *P*-value = 0.720; Table 3).

DISCUSSION

The Centers for Disease Control reports that in 2016, more than 11.5 million people had abused prescription opioids in the past year.[9] In a recent study by Payen et al, it was demonstrated that 90% of ICU patients were treated with opioids, whereas procedural analgesics and nonopioid adjuncts were only used approximately one-third of the time[10,11] The 2 major findings from another retrospective population-based analysis by Howard et al[12] were that opioids are significantly overprescribed after common surgical procedures, and that the quantity of opioid prescribed is associated with higher patient-reported opioid consumption. The opioids-related adverse side effects include sedation, respiratory depression, nausea and vomiting, constipation, hallucinations, confusion, and allergic reactions.[13] Adjunctive agents for pain relief including NSAIDs may be used in combination with opioids to mitigate the side effects of both agents by reducing the total dose required. The American Pain Society advocates the use of MMA, including NSAIDs, for optimal pain control in the treatment of acute traumatic pain (Am Pain Soc).[14]

The potential side effects of opioids, especially in the trauma population, combined with recommendations for a synergistic approach to pain management suggest

TABLE 3. Rescue Medication Usage and Hospital Discharge, mITT Population (0–48 Hours After Dose)

Variables	Placebo (n = 35)	Caldolor (n = 39)	*P*
No. of doses of rescue medication administered			
Mean (SD)	27 (15.8)	23 (18.2)	0.301
Median	27	20	
LS Means (95% CI)	27.2 (21.4 to 32.9)	23.0 (17.5 to 28.5)	
95% CI		−12.2 to 3.8	
Amount of morphine equivalent given (mg)			
Mean (SD)	97 (41.4)	76 (40.1)	0.017*
Median	94	80	
LS Means (95% CI)	97.8 (84.4 to 111.2)	74.9 (62.1 to 87.8)	
95% CI		−41.4 to −4.2	
Time to first narcotic (h)			
n (Number censored)	35 (0)	39 (1)	
Mean (SE)	4.3 (0.8)	6.4 (1.1)	0.046*
Median	3.0	3.5	
95% CI	2.3 to 3.6	2.6 to 6.2	
HR (placebo vs. Caldolor)		1.640	
95% CI for HR		1.009 to 2.665	
Time to discharge (h)			
Mean (SE)	127.4 (19.2)	119.4 (14.1)	0.720
95% CI	61.3 to 118.3	61.9 to 145.6	
HR (placebo vs. Caldolor)		0.914	
95% CI for HR		0.559 to 1.495	

*Denotes significant difference.
LS Means, least-square mean values; CI, confidence interval; SE, standard error.

medications such as IV ibuprofen may be beneficial in treating pain in trauma patients. This approach can help avoid the common complications of opioid-centered analgesia including physical dependence, addiction, and respiratory depression.[15]

The efficacy and safety of IV ibuprofen related to pain management has mainly been studied in postoperative patients after elective procedures. Southworth et al[16] conducted a multicenter, randomized, double-blind, placebo-controlled dose-ranging study of postoperative analgesia to assess the effects of IV ibuprofen versus placebo in 406 patients undergoing orthopedic or abdominal surgery. Kroll et al[17] also performed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of IV ibuprofen in the management of postoperative pain after abdominal hysterectomy. IV ibuprofen was associated with a reduction in morphine requirements over the first 24 hours and resulted in a significant reduction in pain at rest and with movement. Singla et al[18] conducted a multicenter, randomized, double-blind placebo-controlled trial of IV ibuprofen for treatment of pain in postoperative orthopedic adult patients. Administration of IV ibuprofen significantly reduced

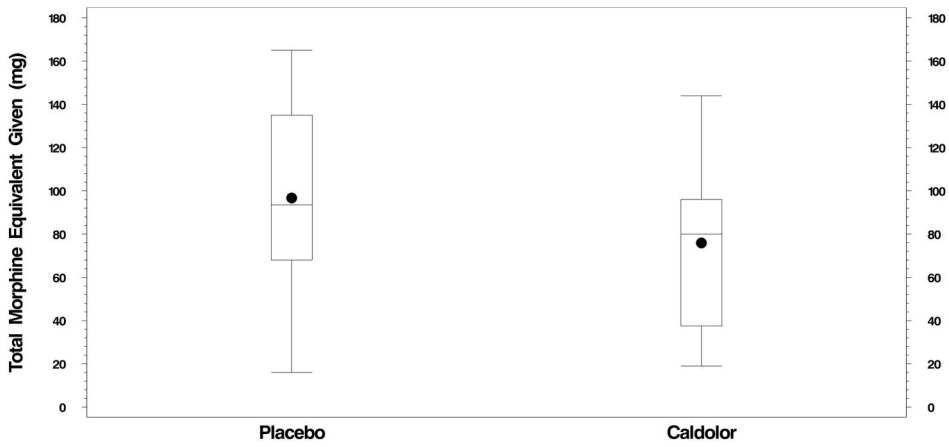

FIGURE 1. Total morphine equivalent given in placebo and Caldolor groups, mITT population.

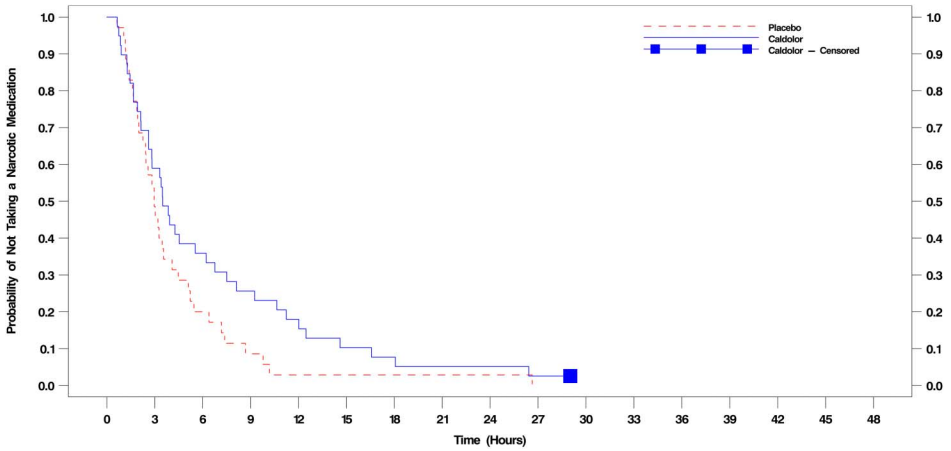

FIGURE 2. Time to first narcotic medication, mITT population. **Editor's Note**: A color image accompanies the online version of this article.

both pain and morphine use in orthopedic patients after elective knee or hip replacement. A retrospective study of IV ibuprofen administration in patients with traumatic rib fracture by Bayouth et al[19] demonstrated that early IV ibuprofen therapy significantly decreases narcotic requirements and results in clinically significant decreases in hospital length of stay. The authors suggested that IV ibuprofen should be given upon admission to augment pain control and recommended a prospective study.[19]

The results of our prospective study demonstrate that Caldolor significantly reduces the amount of opioids that are required to manage pain after a traumatic injury with fracture. In addition, the time to first narcotic medication was longer in the Caldolor group. A placebo patient who has not yet taken a rescue medication is 1.6 times more likely to need a rescue medication than a patient receiving Caldolor. Rescue medication was available to all patients in the study, and the PI scores were analyzed as recorded without any adjustment for the rescue medication. Our findings are in line with previous reports that pain assessment is associated with fewer hypnotics and more nonopioids administration; however, only 42% of ICU patients are assessed for pain.[10,11] PID values were analyzed every 4 hours after start of infusion, and statistically significant difference was observed at 8 hours after infusion. At other time points, mean PID values tended to be higher in the Caldolor group; however, statistical significance was not reached. Overall, pain was managed better in the Caldolor group, as the time for first narcotic medication was longer, and the amount of opioids required to manage pain was significantly less in the Caldolor group as compared to the placebo group, which makes Caldolor a good candidate for managing pain in the trauma population and for reducing the amount of prescription opioids in trauma patients.

LIMITATIONS

The limitations of the study were the single-center experience and the inclusion of a wide variety of orthopaedic trauma patients that might have increased the variability in PI and consequently the unevenness of medication requirements. The strength of the study is in its randomized, double-blind, controlled design, and comparability of study groups that allowed to prevent bias.

CONCLUSIONS

IV ibuprofen provided adequate analgesia, prolonged time to first narcotic administration and was opioid-sparing for the treatment of pain in orthopedic trauma patients, which makes Caldolor a recommended candidate for managing acute pain in the diverse trauma population.

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