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Preemptive Analgesic Effects of Ketorolac in Ankle Fracture Surgery

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Background: **Preemptive analgesia has been difficult to show in human experiments. If ketorolac has preemptive effects, then there may be an advantage to administering it at the beginning of surgery despite the potential for increased blood loss.**

Methods: **The authors performed a randomized, double-blind, controlled trial of 48 patients scheduled for ankle fracture surgery in a county trauma hospital. Anesthesia management was standardized and included adequate opioid analgesia (5 μg/kg fentanyl and 0.1 mg/kg morphine). Intravenous 30 mg ketorolac was administered to 23 patients before tourniquet inflation and to 25 patients after tourniquet inflation. Visual analog scale pain scores, morphine patient-controlled analgesia consumption, nausea–vomiting, and postoperative bleeding were measured.**

Results: **The 23 patients given ketorolac before tourniquet inflation had no increase in pain postoperatively compared with their preoperative baseline ($P = 0.280$). The 25 patients who received ketorolac minutes later after tourniquet inflation had significant increases in their postoperative pain compared with their preoperative baseline ($P = 0.00116$). This effect was short-lived, and by 6 h the pain score in this group was not significantly more than it was preoperatively. Intergroup comparison showed a lower visual analog scale score at 2 ($P = 0.0203$) and 4 h ($P = 0.00549$) in the preemptive group and lower nausea scores at hour 6 ($P = 0.00704$). There was no difference in patient-controlled analgesia consumption between groups.**

Conclusions: **Intravenous 30 mg ketorolac appears to have preemptive analgesic effects in patients undergoing ankle fracture repair. Ketorolac administered before tourniquet inflation prevents postoperative pain being perceived as more intense than preoperative pain.**

THE term "preemptive analgesia" has been used to describe the phenomenon by which analgesia administered before a painful stimulus decreases the intensity of the subsequent pain.[1] This definition was later broadened to include treatment that "prevents the development of hyperexcitability, even if it takes place after surgery."[2] Although clearly demonstrable in animal models, there is little evidence that preemptive analgesia occurs in humans.

To most convincingly show a preemptive analgesic effect, the degree of pain in a group of subjects administered the analgesic before the painful stimulus should be compared with a control group given the equivalent dose of analgesic after the stimulus.[3] In most previous studies of pain after surgery, the prestimulus dose has been administered either before induction or postinduction–preincision, and the poststimulus dose has been administered at the conclusion of surgery. The time delay between the prestimulus and poststimulus doses, however, is a confounding factor. It may obscure any potential preemptive analgesic effect because metabolism of the prestimulus dose during the surgical procedure would produce lower plasma levels of the analgesic at the end of surgery in subjects receiving the prestimulus dose, compared with the poststimulus dose.

In this randomized, double-blind, controlled trial, we examined the effect of ketorolac as a preemptive analgesic for limited orthopedic surgery of the lower extremity, performed with a tourniquet. The prestimulus dose was administered shortly before the tourniquet was inflated, and an equivalent dose was administered immediately after tourniquet inflation. Because ketorolac exerts its analgesic effects primarily at the peripheral level,[4] the latter dose would function as a poststimulus dose because it would not reach the site of action until after the tourniquet was deflated at the end of surgery. Therefore, this study describes a unique model for exploring the potential effects of preemptive analgesia by nonsteroidal anti-inflammatory drugs (NSAIDs) that has circumvented the problem of a significant time delay between administration of the prestimulus and poststimulus doses of analgesic.

Materials and Methods

Subject Selection and Drug Preparation

After obtaining approval from the Institutional Review Board for Human Subject Research (Baylor College of Medicine & Affiliated Hospitals, Houston, TX), written informed consent was obtained from 54 adults with American Society of Anesthesiologists physical status I–II who were scheduled for open reduction and internal fixation of a unilateral ankle fracture. Excluded were subjects with aged less than 16 or more than 65 yr; history of allergy to any NSAID, fentanyl, or morphine; renal dysfunction; coagulopathy; peptic ulcer disease; intravenous drug or ethanol abuse; opioid usage within the preceding 12 h; or NSAID administration within 18 h.

Study Design

Preoperatively, the subjects were randomly assigned to receive ketorolac either before (PRE group) or after

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(POST group) tourniquet inflation, using a computer-generated table of random numbers. Each subject received one 50-ml bag of 0.9% NaCl intravenously after induction while the leg was being prepared and a second 50-ml bag of 0.9% NaCl intravenously immediately after tourniquet inflation. The time interval between administration of these bags was less than 15 min. Only one of the two bags contained 30 mg ketorolac, and the other functioned as a placebo. Subjects in the PRE group received ketorolac before tourniquet inflation and placebo after tourniquet inflation, whereas those in the POST group received placebo before tourniquet inflation and ketorolac after tourniquet inflation. Double-blinding was achieved by having our hospital pharmacy personnel prepare the bags for each subject and label them with the subject's identification number only. The code indicating to which group the subject was assigned was retained by the pharmacy until the conclusion of the study.

Anesthetic Management

Approximately 30 min before induction, all subjects received 30 ml sodium citrate solution orally and 10 mg metoclopramide and 20 mg famotidine intravenously. General anesthesia was induced by intravenous administration of 1–2 mg midazolam, 5 μg/kg fentanyl, and 2 mg/kg propofol. Tracheal intubation was facilitated with a neuromuscular blocking agent, the identity of which was left to the discretion of the attending anesthesiologist. Anesthesia was maintained with sevoflurane and 50–70% nitrous oxide, and additional neuromuscular blocking agent was administered as needed. Twenty to 30 min before skin closure, 0.1 mg/kg of intravenous morphine was administered. Residual neuromuscular blockade was reversed at the conclusion of surgery with intravenous neostigmine (0.05 mg/kg) and sodium glycopyrrolate (0.01 mg/kg). The tourniquet was inflated immediately before skin incision and deflated after the cast was applied at the end of the surgery.

Postoperative Management

Postoperative analgesia was supplied by intravenous morphine using patient-controlled analgesia (PCA) with a 2-mg bolus dose, lockout period of 10 min, 4-h maximum dose of 28 mg, and no basal infusion rate. Nausea and vomiting were treated with 4 mg ondansetron intravenously every 6 h as needed.

Data Collection

Thirty minutes preoperatively, a visual analog scale (VAS) pain score and nausea–vomiting (NV) score were recorded by each subject. The VAS was a 100-mm scale, with 100 signifying the "worst possible pain" and 0 representing "no pain." The NV score was based on the following scale: 1 = no nausea; 2 = mild nausea; 3 = moderate nausea; 4 = severe nausea; and 5 = severe nausea plus vomiting. Postoperatively, at 2, 4, 6, 8, 10, 12, and 24 h after tourniquet inflation, the pain and NV scores were repeated, and the cumulative PCA morphine usage and presence or absence of bleeding at the surgical site were recorded.

Table 1. Demographic Data

	PRE Group (Mean ± SD)	POST Group (Mean ± SD)	*P* Value
Age (yr)	33 ± 13	33 ± 11	0.903
Gender (M/F)	17/8	13/12	0.150
Weight (kg)	83 ± 22	81 ± 23	0.690
Tourniquet time (min)	97 ± 34	92 ± 28	0.573
Succinylcholine usage	6/25	8/29	0.774

Statistics

The sample size was calculated by assuming that a 30% reduction in pain scores or postoperative morphine usage would be a clinically useful effect. This would require 21 patients in each equal group for an α of 0.05 and a 1-β of 0.80 (two-tailed). The data are presented as mean ± 1 SD unless otherwise indicated. The demographic data were analyzed by paired *t* tests and NV data by Kruskall–Wallis one-way analysis of variance. PCA morphine usage and VAS pain scores were analyzed by repeated-measures analysis of variance, with *post hoc* univariate F tests. All tests were performed using Systat 9.0 (SPSS, Inc., Chicago, IL). Statistical significance was defined as $P < 0.05$.

Results

The demographic data for both groups were similar (table 1). Of the 54 subjects enrolled in the study, 6 were eliminated from the study: 2 in the PRE group (one because of malfunction of the tourniquet, and one because of an inadvertent booking of a midfoot fracture as an ankle fracture) and 4 in the POST group (one because of conversion of the surgical procedure to a closed reduction, one because of administration of intravenous fentanyl in the postoperative anesthesia care unit, one because of incorrect timing of study drug administration, and one because of an administrative error). Thus, the final PRE group consisted of 23 subjects, and the POST group was composed of 25 subjects. The muscle relaxant succinylcholine may, by causing muscle pains, skew postoperative pain data. Succinylcholine usage was similar in both groups (table 1).

Visual analog scale pain score data are presented in table 2. Graphic analysis revealed that any postoperative differences were present from 2–4 h only. Accordingly, analysis of variance was performed from preoperatively to hour 6 only. VAS pain scores were significant for PRE *versus* POST at $P = 0.0225$ and were significant for

Table 2. Intergroup VAS Pain Scores

		Time after Tourniquet Inflation					
	Before OR	2 h	4 h	6 h	8 h	10 h	24 h
PRE group	27 ± 28	26 ± 21	23 ± 26	29 ± 29	33 ± 31	28 ± 26	35 ± 30
POST group	18 ± 15	52 ± 30	38 ± 29	29 ± 26	25 ± 22	33 ± 30	31 ± 27
P value	0.981	0.0203*	0.00549*	0.388			

Values are mean ± SD. Visual Analog Scale (VAS) pain scores.

* *P* = significant.

OR = operating room.

change over time at $P = 0.00158$. The PRE group had significantly lower VAS pain scores than the POST group at hour 2 ($P = 0.0203$) and hour 4 ($P = 0.00549$). By hour 6, the intergroup differences were not significant ($P = 0.388$). Intergroup data are presented in table 2. Analysis of the pain scores for the PRE group only indicated that the VAS pain scores at all time periods postoperatively were similar ($P = 0.280$). For the POST group, there were significant differences ($P = 0.00116$), specifically increases at 2 ($P = 0.00373$) and 4 h ($P = 0.0475$), *versus* the preoperative baseline. Morphine usage was similar for the PRE and POST groups (table 3).

The NV score results are shown in table 4. The PRE group showed a lower NV score than the POST group at hour 6 ($P = 0.00704$). Postoperative bleeding was not reported for any subject.

Discussion

Since the earliest surgical procedures, it has been obvious that most types of surgery produce pain in the postoperative period. However, it has only recently become recognized that direct surgical trauma may not be the only causative factor: the human body can amplify the pain, resulting in a situation known as pain hypersensitivity.[1] Injury to tissues has been showed to cause an exaggerated response to noxious stimuli on both a peripheral basis, by reducing the threshold of nociceptor afferent nerve terminals, and at a more central level, by increasing the excitability of second-order sensory neurons in the spinal cord.

Based primarily on the aforementioned observations, the concept of preemptive analgesia has evolved. By administering an analgesic before the painful stimulus, the development of pain hypersensitization may be reduced or abolished, thus resulting in less poststimulus pain. A wide variety of agents have been examined for their possible preemptive analgesic effects, including systemic[5] and neuraxial[6] opioids, systemic[7] and neuraxial ketamine,[8] systemic NSAIDs,[9–11] and neuraxial[8] and regional[12] local anesthetics. With the possible exception of local anesthetics, none has consistently showed such activity in the postsurgical patient.[2]

Methodological problems have been encountered in most of the previous studies examining preemptive analgesia in humans. For example, many have compared an analgesic intervention administered before the painful stimulus, with no intervention at all. This merely represents an increase in total analgesia in the treatment group. Even studies that have compared an equivalent dose of the same analgesic administered before and after the stimulus of surgery have the potential disadvantage of a significant time delay between the administration of the two doses. For analgesics administered intravenously or intramuscularly, metabolism of the prestimulus dose during the surgical procedure would result in lower plasma levels at the end of surgery, thus biasing the study against improved analgesia in the "preemptive" group. The opposite scenario may occur with orally administered drugs, as doses administered at the conclusion of surgery would have no analgesic activity until they are systemically absorbed. Surgery and anesthesia have definite but variable effects on bowel function and oral drug absorption.

In the current study we developed a model that minimized the time delay between the prestimulus and poststimulus doses of analgesic. Using tourniquet inflation as a means to distinguish the prestimulus (before tourniquet inflation) and poststimulus (after tourniquet inflation) treatment groups, the two doses were adminis-

Table 3. PCA Morphine Usage

	Time after Tourniquet Inflation					
	2 h	4 h	6 h	8 h	10 h	24 h
PRE group	53 ± 21	46 ± 31	38 ± 49	24 ± 21	33 ± 26	29 ± 17
POST group	66 ± 11	58 ± 44	36 ± 29	24 ± 30	22 ± 34	27 ± 22

Values represent mean ± SD of morphine usage in $\mu g \cdot kg^{-1} \cdot hr^{-1}$; global analysis of variance not significant.

PCA = patient-controlled analgesia.

Table 4. NV Scores

		Time after Tourniquet Inflation					
	Before OR	2 h	4 h	6 h	8 h	10 h	24 h
PRE group	1 (1–1)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–5)	1 (1–3)	1 (1–2)
POST group	1 (1–2)	1 (1–5)	1 (1–3)	2 (1–5)	1 (1–5)	1 (1–5)	1 (1–5)
P value	0.378	0.829	0.378	0.00704*	0.402	0.248	0.086

Values are median (range) of NV-scores.

* *P* = significant.

NV = nausea–vomiting; OR = operating room.

tered within 15 min of each other. Ketorolac was an integral component of this model. By exerting most of its analgesic effects at the peripheral level (*i.e.*, the area of surgery), the ketorolac administered after tourniquet inflation would not reach its site of action until after the tourniquet was deflated at the conclusion of the surgical procedure.

In addition to the aforementioned considerations, ketorolac has several other features that make it an appealing candidate as a potential preemptive analgesic agent. These include its moderate potency (equivalent to morphine in some studies[13]); ease of administration by the intravenous or intramuscular route; lack of acute tolerance, which may occur with even a single dose of opioid[3]; and lack of significant cardiorespiratory or central nervous system side effects. Its two primary adverse effects, interference with renal and platelet function, should be of negligible significance with careful patient selection. Avoiding ketorolac in patients with other risk factors for renal dysfunction, and limiting its use to procedures with minimal blood loss (such as ankle fracture repairs using a tourniquet), should provide a very acceptable margin of safety.

The current study shows that 30 mg ketorolac administered intravenously before tourniquet inflation has preemptive analgesic effects in subjects having open reduction and internal fixation of ankle fractures. This is most convincingly showed by the observation that the subjects who received ketorolac before the surgical stimulus (PRE group) had no increase in VAS pain scores postoperatively compared with their preoperative score. By contrast, for the POST group subjects, the pain scores for the first 4 h were greater than the preoperative value.

Further evidence supporting a preemptive analgesic effect is derived from the intergroup analysis of VAS pain scores, in which the PRE group had lower pain scores than the POST group 2 and 4 h after tourniquet inflation. Several factors may have contributed to the lack of a demonstrable intergroup difference at later time periods. For example, the 30-mg dose of ketorolac may have been too small to show a persistent intergroup effect. The use of relatively high doses of opioids intraoperatively may have also obscured any potential differences between groups by providing very good analgesia in both groups. Alternatively, the intense opioid analgesia may have prevented postoperative sensitization of spinal neurons that might have swamped the demonstrated, short-lived, preemptive effect of ketorolac. These opioid doses were chosen to simulate the usual clinical practice at our institution and to avoid the potential for poor analgesia on arrival in the postoperative anesthesia care unit. Of course, both fentanyl and morphine do have preemptive effects themselves,[7,8] although both groups received identical opioid analgesia and at the same times. In addition, ketorolac may show some activity at the level of the spinal cord. Although most of the available literature suggests that ketorolac exerts its antiprostaglandin effects primarily at the periphery,[4] and the ratio of plasma to cerebrospinal fluid ketorolac concentration after intramuscular administration is approximately[14] 1000:1, intrathecal ketorolac has shown analgesic activity in a rat model.[15] The POST group would be expected to have similar, or perhaps higher, levels of ketorolac in the cerebrospinal fluid than the PRE group. Finally, only one dose of ketorolac was used. Woolf and Chong[1] suggested that chemical mediators released by the inflammatory reaction to tissue trauma produce continuing nociceptor stimulation and both peripheral and central pain hypersensitization. This inflammatory reaction would persist until wound healing is complete; thus, optimal "preemptive" analgesia may have involved continuing the ketorolac into the postoperative period.

Patient-controlled analgesia morphine usage has been used as a measure of analgesic effectiveness in numerous studies even though it is a surrogate marker.[16] There was a trend toward lower usage for the PRE group at hour 2, but it did not achieve statistical significance. As the timing of ketorolac administration did not significantly affect morphine usage, one would also anticipate that adverse effects associated with morphine would not differ significantly between the PRE and POST groups. Accordingly, the NV scores were similar for both groups at all time intervals postoperatively except one. It is unclear why the PRE group has a lower median NV score than the POST group at 6 h after tourniquet inflation.

The potential preemptive analgesic effects of ketorolac have been previously examined by Rogers *et al.*[9] and Fletcher *et al.*[10] The former group showed lower opioid usage after abdominal hysterectomy in subjects administered 10 mg ketorolac intravenously before skin incision

compared with subjects given ketorolac after skin closure. This effect was only noted at 2 h postoperatively, possibly because of the low dose of ketorolac used. In contrast, Fletcher *et al.* examined the effects of 60 mg intravenous ketorolac injected before induction in subjects undergoing total hip replacement surgery. Compared with the subjects administered ketorolac during skin closure, those who received ketorolac before induction had lower VAS pain scores immediately postoperatively and decreased opioid usage during the first 6 h postoperatively. However, both studies have the potential limitation of the poststimulus dose being administered at, or close to, the conclusion of surgery. In addition, relying on opioid-sparing effects as the main evidence of improved analgesia postoperatively is a potential concern because many other factors may influence PCA opioid usage, including mood, anxiety, expectations of recovery, and perception of support.[17,18] Of further importance was the excessive blood loss reported in the aforementioned studies during both the intraoperative[9] and perioperative[10] periods, respectively. These observations emphasize the need for careful consideration of the type of surgical procedure when using ketorolac.

In conclusion, a single 30-mg dose of ketorolac administered intravenously before tourniquet inflation appears to have preemptive analgesic effects in subjects having open reduction and internal fixation of unilateral ankle fractures. It is a technique that is easy to perform and has minimal risks in this type of limited orthopedic surgery. Furthermore, the demonstration of preemptive analgesic activity in this model supports the view that ketorolac has primarily a peripheral site of action.

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