



Original contribution

# A double-blind prospective comparison of rofecoxib vs ketorolac in reducing postoperative pain after arthroscopic knee surgery<sup>☆</sup>

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## Abstract

**Study Objective:** The aim of this study was to compare the analgesic efficacy of premedication with rofecoxib vs intravenous (IV) ketorolac in reducing postoperative pain after arthroscopic knee surgery.

**Study Design:** This is a prospective, randomized, double-blinded study.

**Setting:** This study was set at a university hospital.

**Subjects:** The subjects include 54 patients with American Society of Anesthesiologists physical statuses I, II, and III undergoing knee arthroscopy.

**Interventions:** Group 1 received 50 mg oral rofecoxib preoperatively with IV placebo injection, which was administered 20 minutes before the end of the operation. Group 2 received a preoperative placebo and 30 mg IV ketorolac 20 minutes before the end of surgery.

**Measurements:** The primary outcome measure was the proportion of patients reporting pain in the postoperative anesthesia care unit, 6 hours and 24 hours after discharge. Additional end points included the use of 5:325 mg oxycodone-acetaminophen (O/A) tablets, pain scores, patient's satisfaction survey, and comparison of side effects. Data were analyzed using independent samples *t* tests for continuous variables or  $\chi^2$  tests for categorical variables.  $P < .05$  was considered significant.

**Results:** The 2 groups were comparable with regard to patient characteristics, intraoperative medication use, and duration of surgery. There was no difference either in pain scores or O/A use in the postoperative anesthesia care unit. At 24 hours after discharge, significantly more patients in the ketorolac group (91%) reported pain than the rofecoxib group (63%) ( $P = .02$ ). Sixty-one percent of patients in the ketorolac group used O/A during the first 24 hours vs 38% in the rofecoxib group. The difference, however, was not statistically significant.

**Conclusion:** Preoperative rofecoxib is as effective as ketorolac for the treatment of pain after knee arthroscopy. Higher frequency of pain reporting at 24 hours by patients in ketorolac group is explained

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by the longer analgesic effect of rofecoxib. Future studies should directly compare gastrointestinal injury of these drugs, as well as cost-effectiveness of rofecoxib vs ketorolac.

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## 1. Introduction

Multimodal pain management (the simultaneous use of analgesics with different mechanism of action) has been recommended for a relief of postoperative pain to reduce opioid consumption by coadministering nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) [1,2]. Ketorolac and opioid analgesic are the usual treatment of postoperative pain relief for knee arthroscopy in our institution. The use of ketorolac, however, is associated with side effects such as bleeding, gastrointestinal (GI) injury, and renal toxicity [3]. It has been suggested that newer NSAIDs that are more specifically inhibit cyclooxygenase (COX)-2 isoenzyme demonstrate analgesic efficacy equivalent to ketorolac while minimizing adverse effects [4].

The aim of this prospective, double-blinded, randomized trial was to examine whether there is any difference in the number of patients reporting pain after 24 hours treated with a COX-2 inhibitor rofecoxib vs ketorolac after arthroscopic knee surgery (primary end point). No studies directly compared analgesic equipotency of these drugs. Secondary outcome variables included 11-point verbal rating pain scale (VRS) and opioid consumption, as well as patient satisfaction.

## 2. Materials and methods

### 2.1. Subjects

A total of 54 adults with a diagnosis of nonrepairable meniscus tear with at most grade I to II chondromalacia scheduled for elective arthroscopic knee surgery volunteered to participate in the study. This particular type of surgery and diagnosis is chosen to limit the variability in postoperative pain from one patient to another. Inclusion criteria were adult patients without significant laboratory abnormalities, American Society of Anesthesiologists (ASA) physical status I to III, and no medical contraindication to anesthesia. Nonsteroidal anti-inflammatory drugs were discontinued 5 to 7 days before surgery in accordance with the institutional policy. No attempts were made to alter other concurrent patient medications.

### 2.2. Study design

Patients were randomized into 2 groups, according to a predetermined random numbers sequence. Baseline VRS scores were evaluated 60 to 90 minutes before surgery. Half of the patients received a preoperative dose of oral rofecoxib (50 mg) 30 to 60 minutes before surgery with a placebo given intravenously (IV) near the end of the operation. The

other half was treated with a preoperative placebo 30 to 60 minutes before surgery and a dose of 30 mg IV ketorolac 20 minutes before the end of surgery. The investigator who was blinded to patient group allocation assessed the intensity of postoperative pain and administered 5:325 mg oxycodone-acetaminophen (O/A). The pain scores were obtained at rest. The goal of postoperative pain management was to achieve VRS score of less than 2.

### 2.3. Anesthetic management

Every patient was monitored according to ASA standards. Each patient received fentanyl (1.4  $\mu\text{g}/\text{kg}$ ), midazolam (0.07 mg/kg), and propofol (70  $\mu\text{g}/\text{kg}$  per minute) for sedation as well as supplemental oxygen throughout the case. The surgeon administered 30 mL of 1% lidocaine into the surgical site before insertion of the trocar. At the end of surgery, the surgeon injected morphine (8 mg) and bupivacaine (25 mg) into the intraarticular space.

### 2.4. Data collection

Pain intensity was evaluated with a visual rating scale (VRS: 0 = no pain to 10 = severe pain). If the VRS score was more than 2, O/A was given up to 3 tablets; meperidine was used for persistent pain. Patients were assessed for pain at 5, 60, and 90 minutes after arrival in the postoperative anesthesia care unit (PACU). The following variables were recorded: VRS score, mean arterial pressure (MAP), and heart rate (HR) in the PACU at 5, 60, and 90 minutes; and the total amount of analgesics and antiemetics in the PACU, as well as discharge time from the PACU. Discharge criteria included regained preoperative level of consciousness, stable vital signs, and respiratory stability, as well as a pain score of less than 2 or "tolerable." In addition, each patient received questionnaires to be completed after discharge from the hospital. The first questionnaire evaluated the analgesic requirements and pain scores at 6 and 24 hours after surgery. A second questionnaire assessed overall satisfaction with the perioperative pain control at 6 and at 24 hours. In addition, we collected information regarding adverse events such as nausea, vomiting, and dizziness over the 24-hour follow-up period. A preaddressed stamped envelope containing the questionnaires was given to all study patients on discharge.

### 2.5. Statistical methods

The sample size estimation was based on detecting a difference between the proportion of patients who experienced pain at 24 hours after surgery. Calculations were performed for a single time point, with no adjustment for

**Table 1** Patient demographic characteristics, anesthesia and PACU times, and intraoperative analgesic and anesthetic dosage requirements in the 2 treatment groups

	Ketorolac	Rofecoxib
Sample size	26	28
Age (y) <sup>a</sup>	43 ± 12	43 ± 13
Sex (% male)	69	71
ASA physical status (%)		
I	54	61
II	42	39
III	4	0
Weight (kg) <sup>a</sup>	82 ± 19	84 ± 15
Fentanyl <sup>a,b</sup>	110 ± 25	106 ± 38
Midazolam <sup>a,b,*</sup>	4.6 ± 1.6	3.8 ± 1.4
Propofol <sup>a,b</sup>	268 ± 195	182 ± 105
Time in PACU (min) <sup>a</sup>	122 ± 22	116 ± 23
Anesthesia time (min) <sup>a</sup>	48 ± 15	46 ± 11
Patients with preoperative		
Pain (n [%]) <sup>c</sup>	3 (12)	8 (29)
VRS of patients in pain <sup>a</sup>	1.3 ± 0.6	2.4 ± 2.1

<sup>a</sup> Values are reported as mean ± SD.

<sup>b</sup> For those patients who received fentanyl (fentanyl, n = 51; midazolam, n = 53; propofol, n = 50).

<sup>c</sup> Any patient with VRS of more than 0.

\*  $P < .05$ .

multiplicity. Between 25 and 30 patients in each treatment group would provide 80% power to detect an approximately 30% difference in the proportion of patients who reported pain at a single point at 2-sided  $\alpha$  of .05, which was considered to be a clinically significant outcome.

**Table 2** Postoperative pain rating outcomes

	Ketorolac n = 26	Rofecoxib n = 28
Pain in PACU at 5 min		
Patients with VRS of >0	5 (19)	9 (32)
VRS of patients in pain	2.6 ± 1.5	2.3 ± 1.1
Pain in PACU at 60 min		
Patients with VRS of >0	9 (35)	12 (43)
VRS of patients in pain	1.9 ± 1.1	2.4 ± 1.9
Pain in PACU at 90 min		
Patients with VRS of >0	8 (31)	11 (39)
VRS of patients in pain	1.9 ± 1.0	2.1 ± 1.3
Pain in PACU at discharge		
Patients with VRS of >0	10 (39)	10 (36)
VRS of patients in pain	1.4 ± 0.5	1.6 ± 0.7
Pain at 6 h <sup>a</sup>	n = 23	n = 24
Patients reported pain	9 (39)	12 (50)
VRS of patients reported pain	3.49	2.00
Pain at 24 h	n = 23	n = 24
Patients reported pain <sup>b</sup>	21 (91)	15 (63)
VRS of patients reported pain	3.32	3.08

Values are presented as n (%) or mean ± SD.

<sup>a</sup> Three patients in the ketorolac group and 4 in the rofecoxib group did not return their questionnaires.

<sup>b</sup>  $P < .05$  ( $\chi^2 = 5.4$ ).

**Table 3** Postoperative analgesic requirements in PACU and after discharge in the 2 treatment groups

	Ketorolac	Rofecoxib
O/A use in PACU	n = 26	n = 28
Patients	4 (15)	2 (7)
No. of tablets per user	1.25 ± 0.3	1.5 ± 0.7
O/A at 6 h after discharge	n = 23	n = 24
Patients	9 (39)	4 (17)
No. of tablets per user	2.4 ± 1.6	1.0 ± 0
O/A at 24 h after discharge	n = 23	n = 24
Patients	14 (61)	9 (38)
No. of tablets per user	2.2 ± 1.6	2.7 ± 1.4

Values are presented as n (%) or mean ± SD.

Independent sample  $t$  tests (for continuous variables) and  $\chi^2$  tests (for categorical variables) were performed on the variables that evaluated differences between groups (eg, demographic variables, proportion of patients reporting pain, VRS scores, amount of analgesic and antiemetic intake).

A 2-factor (group and time) analyses of variance with repeated measures were performed on MAP and HR values, comparing the differences between the rofecoxib and ketorolac groups over time from baseline (preoperatively) and at 4 time points postoperatively. Main effects (differences between the study and comparison group), effects over time, and interaction effects were evaluated.

### 3. Results

There were no statistically significant differences noted between the study and comparison groups on demographics or intraoperative characteristics, except that the ketorolac group received more midazolam intraoperatively (Table 1). A 2-factor repeated measures analysis of variance performed on MAP and HR while in the PACU (at 5, 60, and 90 minutes, and at discharge) showed a significant time effect ( $F = 13.9$ ,  $P < .001$ ) for MAP, reflecting an increase over time for both groups but no significant interaction effects. There were no significant time or interaction effects noted for HR.

Evaluation of postoperative pain showed no differences between the groups while in the PACU with regard to the number of patients who had pain (VRS, >0) or the intensity of their pain ratings (Table 2). There was no difference in

**Table 4** Postoperative side effects

	Ketorolac n = 23	Rofecoxib n = 24
Nausea	7 (30)	3 (13)
Vomiting	0	1 (4)
Dizziness	3 (13)	6 (25)

Values are presented as n (%).

**Table 5** Satisfaction with postoperative pain control

	Ketorolac n = 23	Rofecoxib n = 24
<i>Satisfaction ratings at 6 h</i>		
Excellent	11 (48)	17 (71)
Good or fair	12 (52)	7 (29)
<i>Satisfaction ratings at 24 h<sup>a</sup></i>		
Excellent	7 (30)	15 (63)
Good or fair	16 (70)	9 (38)

Values are presented as n (%).

<sup>a</sup>  $P < .05$  ( $\chi^2 = 4.85$ ).

discharge times from the PACU. At 24 hours postdischarge, however, significantly more patients in the ketorolac group reported pain (91%) than in the rofecoxib group (63%). In addition, there were findings approaching significance at 6 hours postdischarge for patients in the ketorolac group to have more intense pain than in the rofecoxib group ( $P = .07$ ). There were no significant differences in the O/A usage between the 2 groups; however, at 2 of the assessment points, the ketorolac group used more O/A tablets than did the rofecoxib group (Table 3). Similarly, there were no differences in the number of patients who experienced any side effects such as nausea, vomiting, or dizziness (Table 4). With regard to overall satisfaction with postoperative pain control, at 24 hours postdischarge, significantly more patients in the rofecoxib group rated their satisfaction as “excellent” (63%) than in the ketorolac group (30%; Table 5).

#### 4. Discussion

This study compared the analgesic efficacy of premedication with 50 mg rofecoxib with the IV administration of 30 mg ketorolac 20 minutes before the end of surgery in ambulatory patients undergoing knee arthroscopy. We found that premedication with rofecoxib is as effective as ketorolac for the treatment of pain after knee arthroscopy. Both the intensity of pain and time to discharge from the recovery room were not statistically different between the 2 groups studied. Significantly more patients in the ketorolac group reported pain 24 hours after discharge than did those in the rofecoxib group, a finding that correlates with higher overall satisfaction with pain control in rofecoxib group.

Additive or synergistic effects of combining NSAIDs with systemic opioids are well documented in ambulatory surgery [5,6]. In comparing NSAIDs with placebo, most studies show a decrease in postoperative pain scores and/or opioid requirements and fewer side effects during recovery [4,7,8]. In our institution, ketorolac is usually included in the regimen for controlling postoperative pain in knee arthroscopy. The use of ketorolac has been found to reduce morphine consumption by approximately 30% after major

orthopedic procedures [9]. In addition, patients treated with ketorolac had a decreased frequency of postoperative nausea and vomiting, they tolerated oral fluids, and they were judged fit for discharge sooner than were those receiving opioid compounds [7,10].

There is a reluctance to use ketorolac in some patients. Ketorolac, like other nonspecific NSAIDs, inhibits both COX-1 and COX-2 isoenzymes. The COX-1 enzyme is expressed in many tissues and is responsible for mediating routine physiological functions including gastric mucosa and platelet and kidney function [11]. Most of the NSAIDs' adverse effects are related to the inhibition of COX-1 isoform. A postmarketing surveillance study demonstrated an association between ketorolac use and GI and operative site bleeding, especially in older patients [3]. Cases of GI ulceration or bleeding have been reported after a brief use of ketorolac [12,13]. Furthermore, there have been reports of death and renal failure requiring dialysis in otherwise healthy patients who received only 1 dose of ketorolac [14,15].

Cyclooxygenase-2-selective compounds revealed a much lower risk for gastric erosion and ulceration relative to nonspecific NSAIDs while still maintaining an analgesic effect. Furthermore, they are devoid of antiplatelet function, which is characteristic of the nonselective NSAIDs [4,16]. Hence, COX-2 inhibitors may offer a potential advantage over more traditional NSAIDs in the perioperative period, providing their equipotent analgesic effect. There is a paucity of studies, however, that have compared the analgesic equivalency of these 2 classes of medications. To our knowledge, our study is the first direct comparison of rofecoxib and ketorolac.

Rofecoxib and ketorolac have different modes of administration and dosing regimens. The recommended dose of rofecoxib for the treatment of postoperative pain is 50 mg, administered once daily. The median time to maximal concentration is 2 to 3 hours [17]. Hence, patients are commonly pretreated with rofecoxib before surgery. Rofecoxib activity is sustained for 24 hours. The effect of a single dose of ketorolac lasts only 6 hours (either parenteral or oral). The difference in pharmacokinetic profiles explains the more intense pain at 6 hours postdischarge reported by the ketorolac group patients (VRS of 3.5 vs 2.0,  $P = .07$ ).

Patients in both groups were advised to take O/A for pain after discharge as needed. Despite this advice, more patients in the ketorolac group reported pain at 24 hours after discharge. A higher frequency of pain reporting at 24 hours postdischarge in the ketorolac group (91% vs 63%) is probably related to the patient's reluctance to take O/A due to real or perceived side effects (eg, constipation, nausea, sedation).

Patient satisfaction as an outcome measure is a recent focus in health care [18,19]. A patient satisfaction survey measures how well the patient's expectations were met and his or her overall perception of pain management. Although the determination of satisfaction with postoperative pain

generally requires a multidimensional inquiry, a simple, self-reporting scale of global satisfaction is commonly used to grossly compare different pain management strategies. Significantly, more patients in the rofecoxib group rated their satisfaction as "excellent" (63%) than in the ketorolac (30%) group. These results correlate with higher number of patients reporting pain at 24 hours in the ketorolac group.

This study could be criticized for not comparing the study drug with a placebo. However, there are numerous studies that document a reduction in opioid requirement by either ketorolac or rofecoxib [4,5,7-9]. The advantages of perioperative use of NSAIDs are extensively documented, and it is a standard of care in our institution. In recent years, numerous authors, as well as regulatory and research guiding agencies (ie, Food and Drug Administration, World Medical Association Declaration of Helsinki), question and discourage the unethical use of placebo controls [20,21]. In general, inert placebos should not serve as the comparison to a new therapy in any randomization trials. The best available therapy should be offered to patients in an ethical clinical trial. Direct comparison of 2 drugs was consistent with the goal of the study to demonstrate the analgesic equipotency of 2 drugs.

In summary, we conducted a prospective, double-blind comparison of premedication with rofecoxib and intraoperative injection of ketorolac for postoperative pain control. Our results demonstrated the equipotent analgesic efficacy of rofecoxib and ketorolac in patients undergoing knee arthroscopy. Future studies should directly compare adverse effects associated with these drugs, as well as the cost-effectiveness of rofecoxib vs ketorolac.

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