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Corresponding author:

Seihee Min, M.D., Ph.D.

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel: +82-2-3010-3868

Fax: +82-2-540-4892

Email: d250257@amc.seoul.kr

ORCID: <https://orcid.org/0000-0002-0945-0177>



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Opioid-based versus opioid-sparing patient-controlled analgesia using ketorolac and nefopam after total knee arthroplasty: a randomized, double-blind, non-inferiority trial

Jiwon Han¹, Haesun Jung¹, Min Kyoung Kim¹, Yong-Beom Park², Seihee Min³

Departments of ¹Anesthesiology and Pain Medicine, ²Orthopedic Surgery, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong, ³Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Opioids remain widely used for postoperative pain control after total knee arthroplasty (TKA); however, concerns about adverse effects and dependency drive interest in opioid-sparing alternatives. This study evaluated the efficacy and safety of opioid-sparing patient-controlled analgesia (PCA) after TKA.

Methods: In this prospective, randomized, double-blind, non-inferiority study, 98 patients undergoing TKA under spinal anesthesia received either opioid-based PCA (continuous infusion of 1200 µg fentanyl, n = 49) or opioid-sparing PCA (continuous infusion of 150 mg ketorolac tromethamine and 100 mg nefopam hydrochloride, n = 49). Both groups received patient-controlled boluses of 300 µg fentanyl. The primary endpoint was the visual analog scale (VAS) pain score at rest on postoperative day (POD) 1, assessed using a 1.5-point non-inferiority margin. Secondary endpoints included additional analgesics, mobility, postoperative pain at rest and during ambulation, and adverse effects on PODs 1 and 2.

Results: The mean VAS score at rest on POD 1 was 5.45 ± 2.48 in the opioid-based PCA group and 5.90 ± 2.31 in the opioid-sparing PCA group. The mean difference was 0.45 points (95% CI [−0.36 to 1.25]), within the prespecified non-inferiority margin. Pain scores at each time point were non-inferior in the opioid-sparing group, whereas rescue analgesic requirements were significantly reduced on POD 2 (P = 0.006). Nausea and vomiting on POD 1 were more frequent with opioid-based group (34.7% vs. 12.2%, P = 0.009).

Conclusions: Opioid-sparing PCA with ketorolac and nefopam provides non-inferior analgesia to opioid-based PCA, while reducing opioid consumption and drug-related adverse effects after TKA.

Keywords: Analgesia, patient-controlled; Analgesics, non-narcotic; Analgesics, opioid; Arthroplasty, replacement, knee; Opiate substitution treatment; Opioid analgesics; Pain, postoperative; Total knee arthroplasty.

Introduction

Excessive opioid use has emerged as a significant concern in patients undergoing orthopedic surgery. Given that postoperative pain directly affects patient mobility, which is a critical factor in recovery, opioids have been used as primary analgesics, especially fol-

lowing knee surgeries [1–3]. With growing concerns over the global opioid overdose crisis, non-opioid alternatives, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and nefopam, have been recommended for postoperative pain management [4–8]. Nevertheless, opioids remain the preferred choice among orthopedic surgeons due to their potent analgesic effects. To address this issue, implementing an effective opioid-sparing patient-controlled analgesia (PCA) protocol for immediate postoperative pain management is crucial to reduce reliance on opioids.

A dual-chamber PCA pump is a device designed to administer two different analgesics separately: continuous infusion without a bolus function in one chamber and patient-administered bolus doses from the other [9,10]. With this mechanism, postoperative pain control, as well as additional postoperative opioid consumption including the amount self-administered by PCA, can be compared between opioid-based and opioid-sparing protocols. Although several studies have demonstrated effective pain control using opioid-sparing regimens after knee surgery [4–6,11,12], there is a paucity of randomized clinical trials comparing the exclusive postoperative analgesic effects, additional opioid consumption, immediate patient rehabilitation, and adverse effects between opioid-based PCA and opioid-sparing PCA.

Given that the combination of ketorolac and nefopam, as non-opioid alternatives to fentanyl, was expected to provide analgesic efficacy comparable to that of fentanyl, this trial adopted a non-inferiority design to assess the efficacy and safety of an opioid-sparing protocol compared with an opioid-based protocol in patients undergoing total knee arthroplasty (TKA) under spinal anesthesia.

Materials and Methods

Study design and ethical approval

This prospective, randomized, double-blind, non-inferiority trial was approved by the Institutional Review Board of Chung-Ang University Gwangmyeong Hospital (#2210-033-049 on January 6, 2023) and registered at ClinicalTrials.gov (NCT05861791; February 7, 2023) prior to patient enrollment. The study was conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki (revised 2013). All participants provided written informed consent and could withdraw consent at any time.

Study population and randomization

At a single institution, patients (≥ 20 years) with American Society of Anesthesiologists (ASA) physical status I–II scheduled for elective TKA under spinal anesthesia between February 7, 2023, and July 26, 2024, were eligible. Exclusion criteria included previous knee surgery; allergy to study drugs; drug dependence; chronic opioid use; psychotic disorders; impaired hepatic or renal function; history of gastrointestinal ulcer, bleeding, or perforation; risk of urinary retention; bronchial asthma; and contraindications to spinal anesthesia. For patients undergoing bilateral TKA, only data from the first surgery were analyzed.

After obtaining written informed consent, patients were randomized in a 1:1 ratio to receive either opioid-based or opioid-sparing PCA. Randomization was performed by an independent assistant not involved in the study, using a computer-generated online program. Group allocation was concealed in opaque envelopes, and both patients and investigators involved in data collection and analysis were blinded to group assignment.

Anesthesia

Three-lead electrocardiography, noninvasive blood pressure, peripheral oxygen saturation (SpO_2), and electroencephalography monitoring (Sedline, Masimo) were performed. Oxygen was administered at 5 L/min via face mask without premedication. Spinal anesthesia was induced by an investigator who was blinded to group allocation. The patient was placed in the lateral decubitus position, and a 25-gauge Quincke needle was inserted into the subarachnoid space between the L3 and L4 or L4 and L5 intervertebral spaces by midline or paramedian approach. After confirming cerebrospinal fluid backflow, 8–15 mg of 0.5% hyperbaric bupivacaine and 10 μg of fentanyl were slowly injected into the subarachnoid space. The patient was then placed in the supine position with close monitoring of vital signs for immediate adverse events.

The spinal block was assessed by evaluating the sensory level with a cold swab and the motor level by asking the patient to move the legs. Upon confirmation of adequate neuraxial blockade and hemodynamic stability, the patient was sedated by an anesthesiologist not involved in the study using dexmedetomidine at 0.4–0.6 $\mu\text{g}/\text{kg}/\text{h}$ via infusion pump (Infusomat, B. Braun). The intraoperative patient state index was maintained at 60–80 based on electroencephalographic monitoring. Midazolam was administered as needed to ensure adequate sedation. All surgical procedures were performed by a single experienced orthopedic surgeon using a consistent technique. An intraoperative analgesic cocktail

comprising 5 mg morphine, 150 mg ropivacaine (0.75%), and 40 mg triamcinolone diluted in 0.9% sodium chloride was injected into the anterior and posterior articular regions. At the end of the surgery, the level of spinal block was reassessed using a cold swab and documented. The intravenous PCA device was then connected, and the patient was transferred to the post-anesthesia care unit (PACU), followed by transfer to the general ward once hemodynamic stability and alertness were confirmed.

Postoperative pain control

Postoperative pain in the ward was managed using a PCA device, as instructed during preoperative education. A dual-chamber PCA device (Bellomic Duo, Cebika), designed to separately administer a continuous infusion of basal analgesics and patient-controlled bolus analgesics, was used. For opioid-based PCA, 1200 µg of fentanyl was diluted with 0.9% sodium chloride to a total volume of 50 ml and administered as the basal analgesic (Fig. 1A). For opioid-sparing PCA, 150 mg of ketorolac tromethamine and 100 mg of nefopam hydrochloride were diluted with 0.9% sodium chloride to a total volume of 50 ml (Fig. 1B). The doses of ketorolac and nefopam used in the opioid-sparing PCA were based on previously published equianalgesic data indicating

that their combined analgesic efficacy is comparable to that of low-dose opioids. In particular, 150 mg of ketorolac and 100 mg of nefopam together provide an estimated analgesic effect equivalent to approximately 1200 µg of fentanyl [13,14]. These doses are also within the recommended daily maximum limits for each drug (≤ 120 mg/d for ketorolac and ≤ 120 mg/d for nefopam), ensuring both analgesic efficacy and safety for postoperative use. In both protocols, the basal infusion rate was fixed at 1 ml/h (fentanyl 24 µg/h vs. ketorolac tromethamine 3 mg/h and nefopam hydrochloride 2 mg/h). The patient-controlled bolus analgesics for both groups contained 300 µg of fentanyl diluted to a total volume of 30 ml with 0.9% sodium chloride, delivered at 1 ml per bolus (10 µg/bolus), with a lockout time of 10 min. An investigator who was not blinded to group allocation prepared the PCA and connected the device to the patient. Additional analgesia in the ward followed a standardized protocol established by the operating orthopedic surgeon: (1) 650 mg of oral acetaminophen twice daily as needed; (2) rescue opioids, including 37.5 mg of intravenous tramadol, 50 µg of fentanyl, or a 5 µg/h buprenorphine patch, as needed; (3) 1 g of intravenous propacetamol as rescue acetaminophen; and (4) 0.9 mg of intravenous ramosetron as needed.

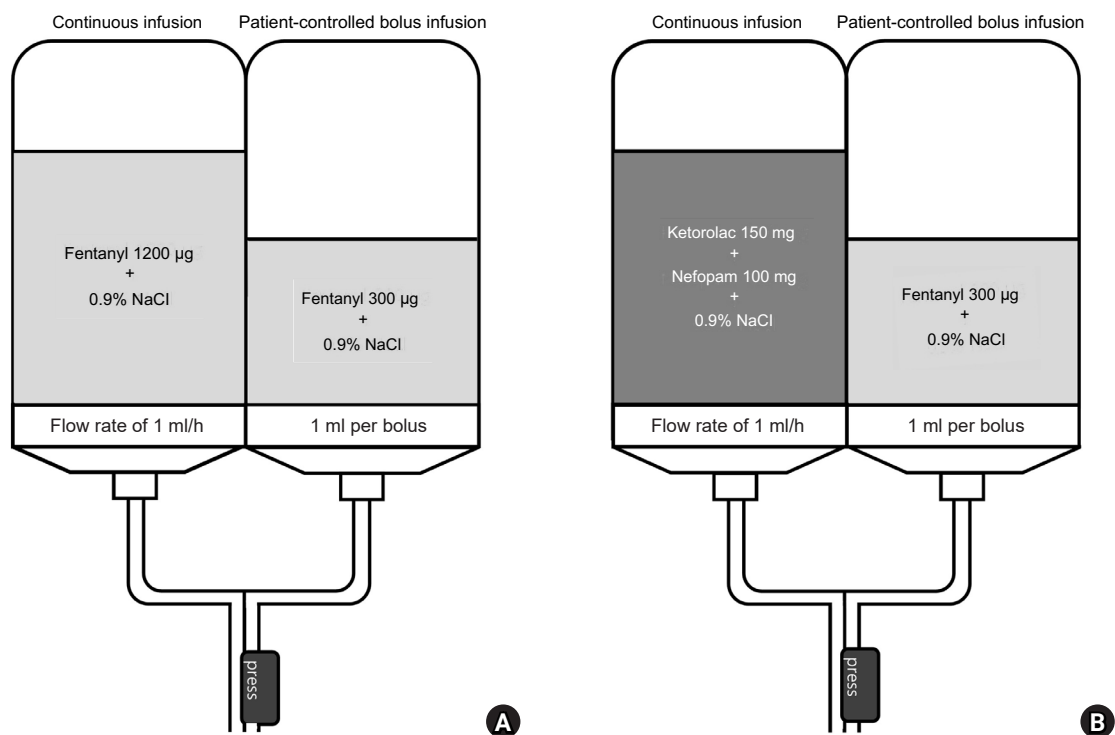


Fig. 1. Schematic diagram of dual chamber PCA device. (A) Opioid-based PCA group. (B) Opioid-sparing PCA group. PCA: patient-controlled analgesia.

Data collection

Data on baseline characteristics, comorbidities, duration of anesthesia and surgery, duration of PACU stay, and length of postoperative hospital stay were collected. The Knee Injury and Osteoarthritis Outcome Score (KOOS) [15] that assesses five domains—pain, symptoms, activities of daily living, sport and recreation functions, and knee-related quality of life—was obtained preoperatively. Intraoperative anesthesia-related parameters, including vital signs, dosage of spinal anesthetics, level of spinal block, and amount of sedatives administered, were recorded. Postoperative pain intensity was assessed using a visual analog scale (VAS), ranging from 0 (no pain) to 10 (worst imaginable pain). VAS scores were recorded both at rest and during ambulation on postoperative days (PODs) 1 and 2. Mobility was evaluated on the same days using a five-point scale (0 = not attempted; 1 = unable to walk; 2 = walking with support; 3 = walking independently with difficulty; and 4 = walking independently without difficulty). The total volume of continuously infused analgesics from the PCA device and the amount of additional analgesic medications administered were recorded. Adverse drug reactions—including postoperative nausea and vomiting (PONV), dizziness, respiratory depression, constipation, urinary retention, renal or hepatic dysfunction, and gastrointestinal bleeding—were also documented. All data were analyzed by two investigators who were blinded to group allocation.

Study endpoints

The primary endpoint was pain intensity at rest on POD 1. Secondary endpoints included pain while walking on POD 1 and pain intensity at rest and while walking on POD 2. Opioid doses administered within the first two PODs were converted to oral morphine equivalents (OMEs) for analysis as follows: 37.5 mg parenteral tramadol = 7.5 mg OME; 50 µg parenteral fentanyl = 15 mg OME; and 5 µg/h buprenorphine patch = 11.5 mg OME. Additional analgesic use, degree of mobility, and drug-related adverse effects during the same period were also analyzed [16].

Sample size calculation and statistical analysis

The sample size was determined through a two-step process. First, we estimated the expected variability in postoperative pain scores using data from Koh et al. [17], who reported a mean VAS pain score of 7.5 ± 2.5 on POD 1 in patients undergoing their first knee replacement in a bilateral TKA cohort. The standard deviation (SD) of 2.5 was used as the input parameter for the

power calculation.

Second, the non-inferiority margin was set at 1.5 points, based on the minimal clinically important difference (MCID) rather than a proportional calculation from baseline values, consistent with generalizable MCID literature specific to TKA. Danoff et al. [18] identified an MCID of 2.26 points for VAS pain after TKA by prospectively correlating pain scores with patient-reported global improvement, defining the smallest change perceived as clinically meaningful. Therefore, the chosen margin represents approximately two-thirds of this MCID, preserving most of the clinically relevant analgesic effect while allowing for only a limited potential loss of efficacy. This approach provides a clinically justified and conservative margin, consistent with regulatory recommendations that non-inferiority thresholds preserve a clinically acceptable fraction of the established effect rather than relying on an arbitrary numeric threshold [19].

The required sample size was calculated to be 44 patients per group based on a non-inferiority margin of 1.5 points, a one-sided α of 0.025, and 80% statistical power. Considering a 10% dropout rate, the final target enrollment was set at 49 patients per group (total, 98).

Normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables are presented as mean $\pm$ SD or median (Q1, Q3), depending on distribution. Categorical variables are presented as counts (percentages). Between-group comparisons of continuous variables were performed using the independent two-sample t-test or Wilcoxon rank-sum test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. All analyses were performed on a per-protocol basis and included all randomized patients who received treatment without discontinuation during the study period. Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) and the T&F program (version 4.0; YooJin BioSoft). Statistical significance was set at $P < 0.05$.

Results

Among the 114 patients screened for eligibility, 16 were excluded due to NSAID allergy, impaired renal function, psychotic disorder, or refusal to participate. Ultimately, 98 patients were equally randomized to the opioid-based PCA group ($n = 49$) and the opioid-sparing PCA group ($n = 49$) (Fig. 2).

Baseline characteristics did not differ significantly between groups (Table 1). Spinal anesthetic levels at the start and end of surgery, as well as the time to transfer from the PACU to the general ward, were also comparable. Furthermore, the intraoperative sedative dose, duration of anesthesia and surgery, PACU stay, and

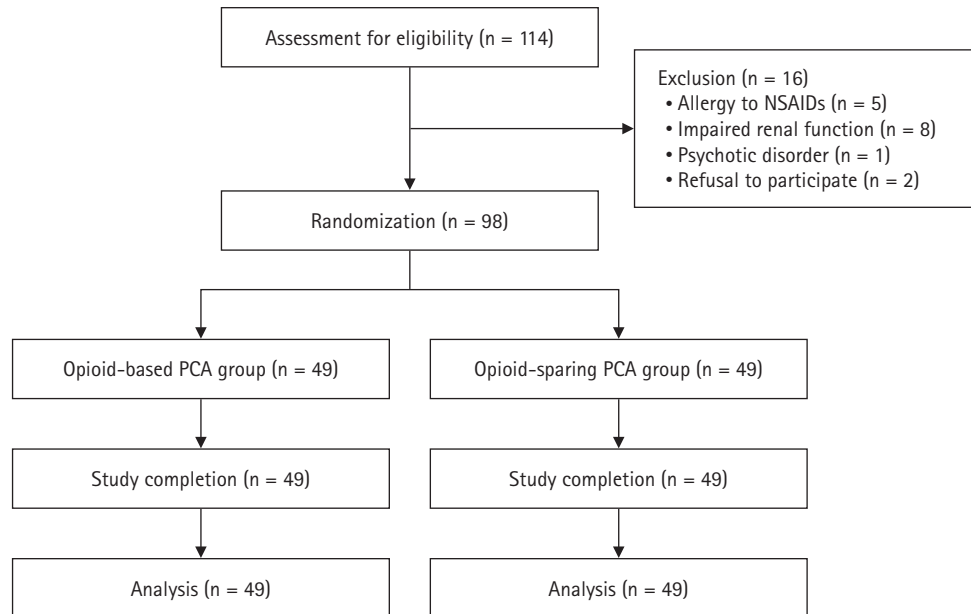


Fig. 2. CONSORT diagram. NSAIDs: non-steroidal anti-inflammatory drugs, PCA: patient-controlled analgesia.

Table 1. Comparison of Patient and Anesthetic Characteristics between the Groups

Variable	Opioid-based PCA group (n = 49)	Opioid-sparing PCA group (n = 49)
Age (yr)	69.9 ± 5.34	70.6 ± 4.99
Height (cm)	155 (150, 158)	155 (151, 159)
Weight (kg)	61.0 (57.6, 70.2)	63.3 (60, 69.5)
Body mass index (BMI) (kg/m ²)	26.7 ± 3.27	27.1 ± 2.87
Sex (M)	11 (22.4)	7 (14.3)
ASA-PS I/II	10 (20.4)/39 (79.6)	1 (2)/48 (98)
Comorbidities		
Hypertension	31 (63.3)	43 (87.8)
Diabetes mellitus	13 (26.5)	4 (8.2)
Cerebral vascular disease	1 (2)	2 (4.1)
Surgical site: right/left	27 (55.1)/22 (44.9)	18 (36.7)/31 (63.3)
KOOS score	103 (89.5, 118)	104 (88.3, 126)
Dexmedetomidine (μg)	91.6 (67.3, 122)	105 (75.1, 142)
Bupivacaine (mg)	11 (9, 12)	10 (10, 11)
Level of spinal block		
At the beginning of surgery	T6 (6, 8)	T7.5 (6, 8)
At the end of surgery	T8 (6, 10)	T8 (6, 10)
At discharge from PACU	T10 (7.75, 10)	T10 (6, 11.3)
Crystalloid (ml)	440 ± 147	408 ± 121
Estimated blood loss (ml)	30 (30, 30)	30 (30, 30)
Operation time (min)	101 ± 28	100 ± 23.7
Anesthesia time (min)	150 (120, 180)	145 (125, 170)
Tourniquet time (min)	100 (70, 120)	100 (70, 120)
PACU stay (min)	35 (30, 45)	35 (30, 45)
Length of hospital stay (days)	15.47 ± 0.82	15.52 ± 0.92

Values are presented as mean ± SD, median (Q1, Q3), or number (%). PCA: patient-controlled analgesia, BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status, PACU: post-anesthesia care unit, KOOS: Knee injury and Osteoarthritis Outcome Score.

length of hospital stay were not significantly different between groups (Table 1).

As the primary outcome, the mean VAS score at rest for the opioid-based PCA group on POD 1 was 5.45 ± 2.48 , whereas the opioid-sparing group had a mean score of 5.90 ± 2.31 . The mean difference was 0.45 points (95% CI, -0.36 to 1.25). The upper limit of this CI (1.25) was below the prespecified non-inferiority margin (1.5), confirming non-inferiority. As secondary outcomes, postoperative pain scores at 30 min (0.10 ± 0.71 vs. 0.08 ± 0.45 , 95% CI $[-0.221$ to $0.180]$, $P < 0.001$), and POD 2 (2.00 ± 1.74 vs. 2.51 ± 2.06 , 95% CI $[-0.131$ to $1.151]$, $P = 0.006$) at rest were non-inferior in the opioid-sparing PCA group compared with the opioid-based PCA group. As shown in Fig. 3, non-inferiority of the opioid-sparing PCA was demonstrated for all time points.

On POD 1, five patients in the opioid-based PCA group and nine in the opioid-sparing PCA group were ambulatory with support. By POD 2, 43 patients in the opioid-based PCA group and 40 in the opioid-sparing PCA group were ambulatory with or without support. The VAS scores during ambulation were also non-inferior in the opioid-sparing PCA group compared with the opioid-based PCA group on POD 2 (4.95 ± 1.57 vs. 4.40 ± 1.57 , 95% CI $[-1.127$ to $0.020]$, $P < 0.001$).

Rescue opioid consumption was numerically higher in the opioid-based group on POD 1 (29.00 [19.00 , 39.00] vs. 21.50 [19.00 , 41.50], $P = 0.329$) and was significantly higher on POD 2 (15.00 [15.00 , 32.50] vs. 15.00 [15.00 , 23.75], $P = 0.006$) (Fig. 4A). The total patient-initiated opioid consumption, comprising self-administered PCA boluses and rescue opioids, was comparable between the two groups on POD 1 and 2 (POD 1: 52.5 [37.5 , 73.5]

vs. 54 [8.25 , 74.5], $P = 0.969$; POD 2: 70 [45 , 80] vs. 67.5 [45 , 90], $P = 0.822$) (Fig. 4B). Additional prescriptions of rescue acetaminophen, analyzed as count data, did not differ significantly between the groups on PODs 1 and 2 (POD 1: 4 [3 , 4] vs. 4 [3.5 , 4], $P = 0.411$; POD 2: 4 [3.5 , 5] vs. 4 [4 , 4], $P = 0.414$). Regarding the opioids included in PCA, the total amount administered within the first two PODs was significantly higher in the opioid-based PCA group, indicating that the opioid-sparing PCA protocol reduced opioid use by more than half (approximately 55%) while maintaining adequate analgesia (POD 1: 135.00 [119.62 , 161.50] vs. 54.00 [38.25 , 76.50], $P < 0.001$; POD 2: 225.00 [220.00 , 255.00] vs. 105.00 [82.50 , 105.00], $P < 0.001$).

The incidence of PONV was higher in the opioid-based PCA group than in the opioid-sparing PCA group on POD 1 ($17/49$ [34.7%] vs. $6/49$ [12.2%], respectively; $P = 0.009$). No other drug-related adverse effects or complications requiring further treatment differed significantly between the groups (Table 2).

Discussion

This study demonstrated that the opioid-sparing PCA protocol was non-inferior to the opioid-based PCA protocol in terms of postoperative pain control, while significantly reducing additional opioid consumption and opioid-related adverse effects following TKA.

Pain management remains a critical component of postoperative patient care. In particular, inadequately controlled postoperative pain in orthopedic surgery patients may lead to impaired mobility, delayed rehabilitation and recovery, increased risk of com-

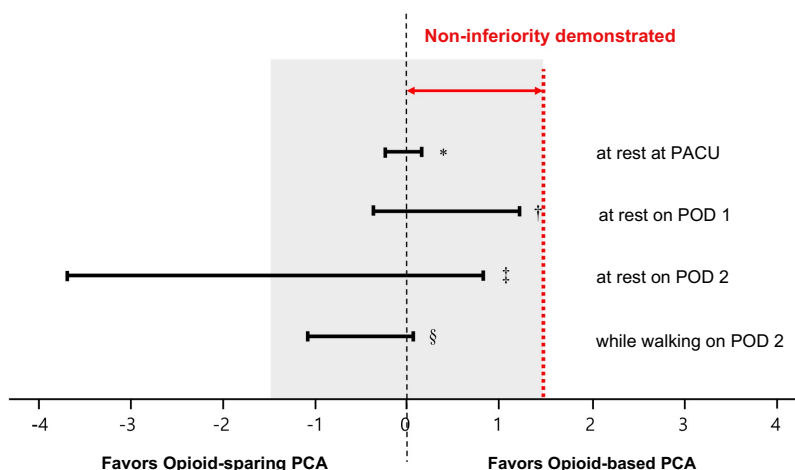


Fig. 3. Forest plot showing between-group differences in postoperative pain intensity (VAS). Each bar represents the mean difference (opioid-sparing PCA minus opioid-based PCA) with 95% CIs at each assessment time: at rest in the PACU, at rest on POD 1 (primary outcome), at rest on POD 2, and during ambulation on POD 2. VAS: visual analog scale, PCA: patient-controlled analgesia, PACU: post-anesthesia care unit, POD: postoperative day. * $P < 0.001$, † $P = 0.016$, ‡ $P = 0.006$, § $P < 0.001$ for non-inferiority test.

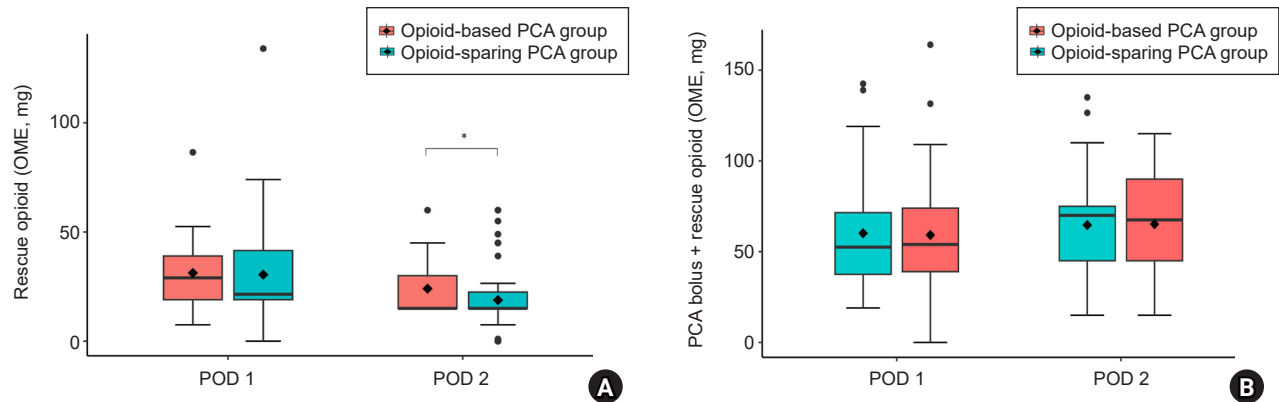


Fig. 4. (A) Total amount of rescue opioid consumed on POD 1 and POD 2. * $P = 0.006$ compared with the opioid-based PCA group, Wilcoxon rank-sum test. (B) The total patient-initiated opioid consumption, comprising self-administered PCA boluses and rescue opioids on POD 1 and 2. POD: postoperative day, PCA: patient-controlled analgesia.

Table 2. Comparison of Drug-related Adverse Effects on PODs 1 and 2 between the Groups

Variable	Opioid-based PCA group (n = 49)	Opioid-sparing PCA group (n = 49)	Relative risks (95% CI)	P value
POD 1				
PONV	17 (34.7)	6 (12.5)	0.35 (0.15–0.82)	0.009
Drowsiness	2 (4.1)	0 (0)	0.2 (0.01–4.06)	0.153
Dizziness	2 (4.1)	0 (0)	0.2 (0.01–4.06)	0.153
Constipation	3 (6.1)	3 (6.1)	1.0 (0.21–4.71)	1.000
Urinary retention	2 (4.1)	1 (2)	0.5 (0.05–5.34)	0.558
Acute kidney injury	0 (0)	1 (2)	3.0 (0.13–71.89)	0.315
Hepatic injury	0 (0)	0 (0)	NE	
Number of complications	22 (44.9)	8 (16.3)	0.36 (0.18–0.74)	0.002
PCA discontinuation	2 (4.1)	0 (0)	0.2 (0.01–4.06)	0.153
POD 2				
PONV	4 (8.2)	0 (0)	0.11 (0.01–2.01)	0.041
Drowsiness	1 (2)	1 (2)	1.0 (0.06–15.54)	1.000
Dizziness	0 (0)	1 (2)	3.0 (0.13–71.89)	0.315
Constipation	1 (2)	2 (4.1)	2.0 (0.19–21.34)	0.558
Urinary retention	1 (2)	0 (0)	0.33 (0.01–7.99)	0.315
Acute kidney injury	0 (0)	0 (0)	NE	
Hepatic injury	1 (2)	1 (2)	1.0 (0.06–15.54)	1.000
Number of complications	8 (16.3)	4 (8.2)	0.5 (0.16–1.55)	0.218
PCA discontinuation	0 (0)	0 (0)	NE	

POD: postoperative day, PCA: patient-controlled analgesia, PONV: postoperative nausea and vomiting, NE, not estimable. Some patients experienced more than one complication; therefore, the sum of individual categories may exceed the total number of patients who experienced complications. Relative risks were calculated for the opioid-sparing PCA group relative to the opioid-based PCA group.

plications, psychological distress, and progression to chronic pain [4,20–22]. TKA is considered one of the most painful surgical procedures, with peak pain scores typically ranging from 5 to 6 on the Numerical Rating Scale on POD 1, despite the use of various analgesic strategies [23–25]. Consequently, opioid prescriptions by orthopedic surgeons remain relatively high, despite evolving pain management approaches aimed at addressing the global opi-

oid crisis [1,11].

Following the widespread introduction of opioids as potent analgesics in medical practice, excessive opioid usage was eventually understood to be possibly more detrimental to overall outcomes, in addition to the associated risks of dependence and overuse [9,26,27]. Moreover, opioid-based analgesia warrants caution, especially in opioid-naïve patients, as it may increase the risk of

long-term opioid dependence. A previous study demonstrated that 1.4% of opioid-naïve patients who underwent TKA developed chronic opioid use postoperatively [28]. Given these considerations, effective management of postoperative pain using non-opioid analgesic strategies may offer long-term benefits by mitigating opioid-related risks.

Modern anesthetic practice has therefore shifted toward opioid-sparing strategies, often using a multimodal approach to manage pain. Recent clinical studies suggest that opioid-free or opioid-sparing anesthesia can provide equivalent analgesia while reducing opioid-related adverse effects such as PONV, respiratory depression, ileus, and urinary retention [10,29–31]. Several studies have also demonstrated effective management of surgical stimuli with hypnotics or analgesics, including intravenous acetaminophen, NSAIDs, ketamine, and alpha-2 agonists (e.g., dexmedetomidine, clonidine, or in combination), as opioid alternatives to achieve opioid-free or opioid-sparing anesthesia [8,9,31–33].

Although multimodal analgesia is now widely recommended, its multi-agent nature makes it difficult to distinguish the intrinsic analgesic contribution of each component. To address this gap, our study was designed to directly compare the pharmacologic analgesic effects of opioid- versus non-opioid-based basal PCA infusions under controlled conditions. This approach allowed us to evaluate whether non-opioid agents alone could provide analgesia comparable to opioids, a question that remains clinically relevant given the persistent variability in postoperative PCA practices across institutions.

To mitigate the adverse effects of opioids and avoid the limitations of single-agent analgesia, multimodal techniques including PCA and peripheral nerve blocks are commonly used to deliver opioid-sparing or opioid-free anesthesia [30,34,35]. Among these, peripheral nerve blocks—particularly femoral nerve block (FNB) and adductor canal block (ACB)—are widely recommended as components of multimodal analgesia in patients undergoing TKA. However, recent systematic reviews and meta-analyses have raised concerns regarding their impact on early postoperative recovery [36–39]. Although FNBs can provide effective pain control, it has been associated with impaired early mobilization due to quadriceps muscle weakness and offers only limited additional analgesic benefit. While ACB provides comparable analgesia to FNB and better preserves quadriceps strength, current evidence suggests it has minimal or no significant effect on early clinical outcomes in patients undergoing TKA under spinal anesthesia with periarticular anesthetic injection [40–42]. These findings indicate that while peripheral nerve blocks are effective for postoperative analgesia, they may hinder early ambulation and functional recovery without offering a significant advantage over systemic multimodal analge-

sia in the context of contemporary TKA protocols. Accordingly, we designed the present study to evaluate the analgesic efficacy of systemic non-opioid agents delivered via PCA in combination with spinal anesthesia and periarticular injection, aiming to reduce opioid use while promoting early rehabilitation.

In this study, we used a combination of ketorolac and nefopam as opioid-sparing analgesics. Ketorolac, an NSAID with relatively potent analgesic effects, inhibits the conversion of arachidonic acid to prostaglandins, thereby blocking pain-associated inflammatory processes at the cellular level. Several studies have demonstrated the efficacy of ketorolac in managing mild-to-severe postoperative pain [43]. Nefopam, a centrally acting non-opioid analgesic derived from non-sedative benzoxazine, is approved and widely used in Europe and Asia. It mediates its analgesic effect by inhibiting the reuptake of serotonin, norepinephrine, and dopamine, and by reducing postsynaptic activation of N-methyl-D-aspartate receptors [44–46]. Therefore, we combined ketorolac and nefopam in the PCA to achieve synergistic analgesia by targeting multiple pain pathways, while minimizing the ceiling effect and toxicity risks associated with NSAIDs. Based on previous studies, both drugs were calculated and administered at equipotent doses to fentanyl within the safety margins to ensure effective and safe administration [46–48]. Consequently, the opioid-sparing PCA group demonstrated not only non-inferior pain control, but also lower postoperative opioid consumption and reduced opioid-related adverse events.

One notable aspect of this study is that the use of a dual-chamber PCA device enabled a direct comparison of opioid and non-opioid analgesics. In conventional PCA systems, both continuous and self-administered bolus infusions consist of the same medication. However, a dual-chamber PCA device allows continuous administration of either opioid-based or non-opioid analgesics, as prescribed by the anesthesiologist, while permitting patients to self-administer opioids as needed for breakthrough postoperative pain. This approach provided clinically effective pain control while minimizing opioid-related adverse effects. Interestingly, two patients in the opioid-based PCA group discontinued PCA on POD 1 due to PONV, whereas no early discontinuation occurred in the opioid-sparing PCA group.

The selection of an appropriate non-inferiority margin is critical to the validity of trial conclusions. Our margin of 1.5 points was primarily justified based on established MCID literature rather than on proportional calculations from baseline pain scores. Danoff et al. [18] identified an MCID of 2.26 points for VAS pain after TKA through prospective correlation of pain scores with patient-reported global improvement. Importantly, the actual results support the clinical validity of this margin. The observed mean

difference in pain scores between groups was 0.45 points (95% CI [-0.36 to 1.25]) that corresponds to only 20% of the MCID. This indicates that the pain difference was not clinically perceptible to patients. Even the upper confidence limit (1.25 points) represented only 55% of the MCID, remaining below the threshold associated with a meaningful perceptual change. This interpretation is further supported by the absence of significant differences in patient satisfaction scores and functional recovery milestones between groups.

The clinical validity of the non-inferiority conclusion is further reinforced by the substantial advantages observed with the opioid-sparing approach. Patients in this group showed significantly reduced opioid consumption, a lower incidence of opioid-related adverse effects—including PONV and sedation—and a potentially decreased risk of long-term dependence, while maintaining pain control that was both statistically and clinically comparable to the opioid-based regimen. From a patient-centered perspective, an imperceptible difference in pain (mean, 0.45 points; below the MCID) accompanied by clinically meaningful reductions in treatment-related morbidity represents a favorable risk-benefit balance. This balance is particularly relevant in the current health-care context emphasizing opioid stewardship and Enhanced Recovery After Surgery (ERAS) protocols.

This study has some limitations. First, despite random allocation, the proportion of patients with ASA physical status II was higher in the opioid-sparing PCA group than in the opioid-based PCA group (79.6% vs. 98%, $P = 0.004$). However, postoperative VAS scores were not inferior in the opioid-based PCA group. A higher ASA physical status is associated with more severe postoperative pain in patients undergoing TKA [3]. Therefore, had the general condition of patients been equivalent across groups, the analgesic effect of the opioid-sparing protocol might have been more pronounced. Second, the reference study used to estimate pain score variability involved bilateral TKA [17], whereas we enrolled only patients undergoing their first knee surgery to minimize this concern. Although the pain experience during the first-knee procedure is considered clinically comparable to unilateral TKA in published literature, ideally, reference data should originate from a purely unilateral cohort. Third, the relatively high and similar VAS scores between groups may raise concerns regarding potential loss of assay sensitivity; however, this is more likely to reflect the inherently painful nature of TKA in the immediate postoperative period, as reported in previous studies, rather than a true lack of difference in analgesic efficacy [24,25]. Fourth, although we compared in-hospital opioid consumption, data on long-term opioid prescriptions or patient requests were unavailable. Additionally, ketorolac use is recommended for a maximum

of five days due to the risk of renal toxicity [43]. Fifth, the analgesic regimens used in this trial do not fully reflect contemporary guideline-based multimodal analgesia practices that generally discourage continuous basal opioid infusion and recommend scheduled systemic administration of non-opioid agents. This study intentionally isolated the basal infusion component to directly compare the intrinsic analgesic effects of opioid versus non-opioid agents using a dual-chamber PCA device. However, this design may limit the generalizability of our findings to ERAS protocols. Finally, although non-inferiority trials are valuable for evaluating treatments with potential safety advantages, they are inherently limited in detecting small superiority effects. Our study was specifically powered to demonstrate non-inferiority that was appropriate for addressing the clinically relevant research question, given the evident safety advantages of the opioid-sparing approach and the subclinical magnitude of the observed pain difference. Future studies integrating guideline-concordant multimodal strategies are warranted to confirm the applicability of these results in broader clinical settings beyond this period.

In conclusion, compared with opioid-based PCA, opioid-sparing PCA with ketorolac and nefopam achieved non-inferior postoperative pain control and was superior in reducing additional opioid consumption and drug-related adverse effects in patients undergoing TKA. To address the global challenge of opioid consumption, long-term evaluations of additional opioid consumption and drug-related adverse effects associated with opioid-sparing regimens for immediate postoperative pain control are warranted.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Jiwon Han (Conceptualization; Data curation; Formal analysis; Methodology; Software; Visualization; Writing – original draft)

Haesun Jung (Data curation; Software; Visualization; Writing – review & editing)

Min Kyoung Kim (Data curation; Formal analysis; Resources; Validation; Writing – review & editing)

Yong-Beom Park (Methodology; Resources; Writing – review & editing)

Seihee Min (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

ORCID

Jiwon Han, <https://orcid.org/0000-0002-7828-618X>

Haesun Jung, <https://orcid.org/0000-0002-4928-6930>

Min Kyoung Kim, <https://orcid.org/0000-0003-0477-2588>

Yong-Beom Park, <https://orcid.org/0000-0002-3741-2311>

Seihee Min, <https://orcid.org/0000-0002-0945-0177>

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