



Morphine-Sparing Effect of Intermittent Versus Continuous Intravenous Infusion of Nefopam in Patients After Total Knee Arthroplasty: A Randomized Trial

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Background: Nefopam, a nonopioid analgesic, is recommended to improve pain control and minimize opioid-related side effects following total knee arthroplasty (TKA).

Objectives: To compare cumulative morphine consumption between intermittent infusion (II) and continuous infusion (CI) of nefopam, combined with other multimodal analgesics, in TKA patients.

Methods: Fifty-eight patients were randomly assigned to receive either intermittent nefopam infusion (II group) (20 mg IV every 6 hours) or continuous infusion (CI group) (80 mg/day). The primary outcome was cumulative morphine consumption via patient-controlled analgesia, with secondary outcomes including pain scores every 4 hours and adverse drug reactions (ADRs).

Results: No significant difference was found in cumulative morphine consumption (median [range], 4 [0 - 12] mg in II and 6 [0 - 18] mg in CI; $P = .579$) and the ADRs over 48 hours between groups. At 4 hours, the II group had significantly lower pain scores compared to the CI group (median [range], 0 [0 - 4] and 0 [0 - 8]; $P = .008$). However, by 24 and 36 hours, the CI group reported significantly lower pain scores compared to the II group; median (range), 0 (0 - 5) vs 2 (0 - 9) at 24 hours ($P = .020$) and 0 (0 - 4) vs 2 (0 - 8) at 36 hours ($P = .014$).

Conclusions: Both intermittent and continuous nefopam infusion in primary TKA showed no significant difference in morphine-sparing or occurrence of ADRs within the 48-hour follow-up period. These findings suggest that both infusion methods are comparable in managing post-operative pain in TKA patients.

Keywords: Nefopam, Morphine-sparing effect, Total knee arthroplasty, Intravenous infusion, Multimodal analgesia

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Introduction

Total knee arthroplasty (TKA) is indicated for patients with knee osteoarthritis who are not responding to prior treatment (rehabilitation, medications).^{1,2} TKA is an operation that causes major pain after surgery.³ Postoperative analgesia is required to improve recovery and quality of life and prevent chronic pain. Several studies and published literature have recommended multimodal analgesia for postoperative pain.⁴ Recent guidelines have recommended combinations of regional anesthesia, local infiltration analgesia, and oral analgesia (paracetamol and nonsteroidal anti-inflammatory drugs [NSAIDs] or cyclo-oxygenase-2-specific inhibitors).⁵ However, in 2020, the Acute Pain Service (APS) at Ramathibodi Hospital found that despite receiving multimodal analgesia according to guidelines, 30% to 50% of postoperative TKA patients still experienced moderate to severe pain. For better pain control, nefopam, a medication with different mechanisms and fewer side effects than opioids, has effectively reduced postoperative morphine consumption in TKA patients.^{6,7}

Nefopam, a centrally acting nonopioid analgesic, which is effective for both nociceptive and neuropathic pain,⁸ is associated with lower risks of gastrointestinal and renal side effects compared to NSAIDs, and lacks the respiratory depression risk of opioids.^{9,10} Intravenous (IV) nefopam is indicated for acute postoperative pain control. To minimize side effects such as nausea, vomiting, sweating, and tachycardia from rapid infusion, it is recommended to administer 20 mg IV nefopam slowly over 30 to 60 minutes (intermittent infusion, II) or as a continuous infusion (CI) of 60 to 120 mg per day.⁸ Ramathibodi Hospital has included both the II and the CI regimens in postoperative pain management for patients undergoing TKA.

Prior randomized controlled trials (RCTs) of IV nefopam have shown that it reduces morphine consumption as an II in total hip arthroplasty and hepatic resection (20%¹¹ and 50%¹² reduction, respectively). For CI nefopam,

studies in laparotomy and TKA patients showed reductions of approximately 30%¹³ and 37%,⁷ respectively. However, a study in urological surgery¹⁴ found no difference in morphine consumption at 48 hours between nefopam and placebo groups. The variations in morphine reduction between II and CI methods observed in prior RCTs may be influenced by differences in surgical procedures, leading to varying levels of pain and morphine consumption requirements. Additionally, the pharmacokinetics of II and CI differ significantly; CI maintains a steady serum level without peaks, whereas II may result in subtherapeutic serum levels, especially before the next dose.¹⁵ These pharmacokinetic differences can impact the morphine-sparing effect between the 2 methods. Therefore, this study aimed to compare the effectiveness of different administrations of nefopam in morphine-sparing effects between II and CI of nefopam in combination with other multimodal analgesia in patients undergoing TKA. CI nefopam was hypothesized to reduce morphine consumption comparably to II nefopam.

Methods

Participants

Between March 2021 and October 2022, the study enrolled patients aged 18 to 85 with Kellgren and Lawrence grade 3 to 4 osteoarthritis of the knee,¹⁶ who underwent primary unilateral TKA and weighed at least 45 kg.

The exclusion criteria included patients with a seizure disorder or a history of seizures, benign prostatic hypertrophy or urinary tract abnormalities, narrow-angle glaucoma, cardiovascular and cerebrovascular diseases, creatinine clearance less than 30 mL/min, impaired hepatic function, current use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), psychiatric conditions, allergies to any study medications, and prior opioid use exceeding 2 weeks within the last month.



Study Design

This study was a prospective randomized trial. Eligible patients were randomly allocated in a 1:1 ratio through a computerized block-of-4 randomization process to either receive nefopam 20 mg IV every 6 hours or 80 mg continuous infusion of nefopam over 24 hours, administered postoperatively for 48 hours. The randomization was executed by the researcher, with the allocation outcomes being concealed within white envelopes.

Administration of Analgesic Medications

Following IV cannula insertion, patients received a dose of 2 to 5 mg of midazolam. A specialized anesthesiologist then administered a femoral triangle block. The procedure entailed positioning the patient supine with the leg designated for surgery slightly bent and externally rotated. A linear transducer was placed perpendicular to the long axis of the thigh to identify the proximal end of the adductor canal, as well as the apex of the femoral triangle, marked by the confluence of the medial borders of the sartorius and adductor longus muscles.

Once the appropriate location for the block was determined, the injection site was cleaned and sterilized. A 22-gauge 80-mm Stimuplex® D needle (B. Braun, Melsungen, Germany) was inserted in an anterolateral-to-posteromedial direction through the sartorius muscle until the final needle tip was located superolateral (at 2 o'clock for a left knee and 10 o'clock for a right knee) to the superficial femoral artery and immediately deep to the vastofemoral or vastoadductor membrane that surrounds the posterior part of the sartorius muscle.

The needle's tip was accurately positioned superolateral to the superficial femoral artery – at approximately 2 o'clock for the left knee and 10 o'clock for the right knee – and immediately beneath the vastoadductor membrane encasing the sartorius muscle's posterior. To perform hydrodissection, 2 to 3 mL of normal

saline was injected through the needle into the correct location within the femoral triangle. Then, 20 mL of 0.5% bupivacaine was slowly injected through the needle after ensuring no blood retraction to encircle the femoral artery with the anesthetic. The block's effectiveness the knee's anterior and middle regions, beneath the kneecap, or the inner aspect of the lower leg within 20 minutes postinjection.

During the intraoperative period following the block, the patient received spinal anesthesia with 2.5 to 3 mL of 0.5% isobaric bupivacaine at the L2-L3 or L3-L4 intervertebral space. A tourniquet was used for all patients. Only one orthopedic surgeon performed all surgical procedures via a medial parapatellar approach. Periarticular infiltration (PAI) with 0.5% bupivacaine 20 mL and ketorolac 30 mg in a total volume of 40 mL was performed at the surgeon's discretion.

After surgery, patients were transferred to the postanesthesia care unit (PACU). An IV patient-controlled analgesia (PCA) device with morphine was inserted. The concealed white envelopes containing the random allocation outcome were opened. Then, patients were randomly assigned to receive either nefopam 20 mg (diluted with 100 mL of normal saline solution [NSS]) IV drip over 1 hour every 6 hours or nefopam 80 mg (diluted with 500 mL of NSS) continuous infusion over 24 hours. These assignments were performed by the anesthesiologist. Both regimens were administered for 48 hours. The first dose of nefopam at the PACU was marked as the start time of the study period (time zero; T = 0).

The postoperative oral analgesic regimen was acetaminophen 500 mg, 1 tab every 6 hours, acetaminophen with codeine (325 mg/15 mg), 1 tab once a day, etoricoxib 90 mg, 1 tab at bedtime, and pregabalin 75 mg, 1 tab at bedtime. For breakthrough pain, an IV PCA device with morphine 1 mg/mL, a 1 mg bolus, and a 5-minute lockout time was used.



Rehabilitation Protocol

In the 48-hour study period, all patients adhered to the following rehabilitation protocol:

- Day 0 (Operative day, 0 - 24 hours): After evaluating that the spinal block had dissipated, patients were instructed to begin performing ankle pumping exercises. They were instructed to perform 30 repetitions of ankle pumping for both ankles, 3 times a day.

- Day 1 (25 - 48 hours): Patients continued the ankle pumping exercises and started quadriceps exercises for both legs, performing 10 repetitions, 4 times a day.

Postoperative Management and Evaluation

Pain scores were evaluated using the Numeric Rating Scale (NRS) upon the patient's arrival at the PACU and every 4 hours. In the intermittent group, pain scores were also recorded before administering each subsequent dose of nefopam. Morphine consumption via a PCA device was also recorded. The PCA device was discontinued at 48 hours in all patients. Adverse drug reactions were monitored and recorded during the 48-hour observation period.

The primary outcome in this study was cumulative morphine consumption in the 48-hour study period from a PCA device. Secondary outcomes were pain score every 4 hours and adverse drug reactions.

This study collected all data from nursing records in patients' charts, using a data collection form approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital. The investigator who collected the data was blinded, and all the data was sent to the outcome assessor.

Statistical Analysis

Since there had been no previous study directly comparing the effectiveness of nefopam in reducing morphine consumption between the II and CI groups, this study derived the effect size from the morphine

consumption data of the II and CI studies (mean [standard deviation, SD], 21 [13.5]¹¹ and 39 [28]¹³ mg, respectively) at a significance level of .05 and a power of detection of 80%, and calculated using the G*Power program version 3.1.9.4.¹⁷ Based on these calculations, a sample size of 52 patients (at least 26 patients per group) was necessary. Accounting for a dropout rate of 10%, the final required sample size was determined to be 58 patients.

In this study, intention-to-treat analysis was performed. For patients who experienced an adverse drug reactions (ADRs) that led to discontinuation, this study utilized the last observation carried forward (LOCF) method to handle missing data.

Categorical variables were expressed as numbers with percentages. Continuous variables were expressed as mean with SD for normal distribution, and median with ranges for nonnormal distribution. The significant differences between the 2 groups were determined using the student's *t* test or the Mann-Whitney *U* test for continuous data, the chi-square test, or Fisher exact test for categorical data. Statistical significance was considered at *P* value below .05 ($P \leq .05$) for 2-tailed tests. In statistical analysis, SPSS Statistics version 26.0 was utilized (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; 2019).

Results

Between March 2021 and October 2022, a total of 58 patients participated in this study, with 28 patients assigned to the II group and 30 patients to the CI group. Due to ADRs, 3 patients discontinued nefopam prior to completing the 48-hour study duration; this included 1 patient from the II group and 2 patients from the CI group (Figure 1).

There were no statistically significant differences in patient characteristics between the 2 groups (Table 1).



Cumulative Morphine Consumption

There were no significant differences in cumulative morphine consumption in 48 hours between the 2 groups (median [range], 4 [0-12] mg in the II group and 6 [0-18] mg in the CI group; $P = .579$) (Table 2).

Pain Scores Every 4 Hours After the First Dose of Nefopam

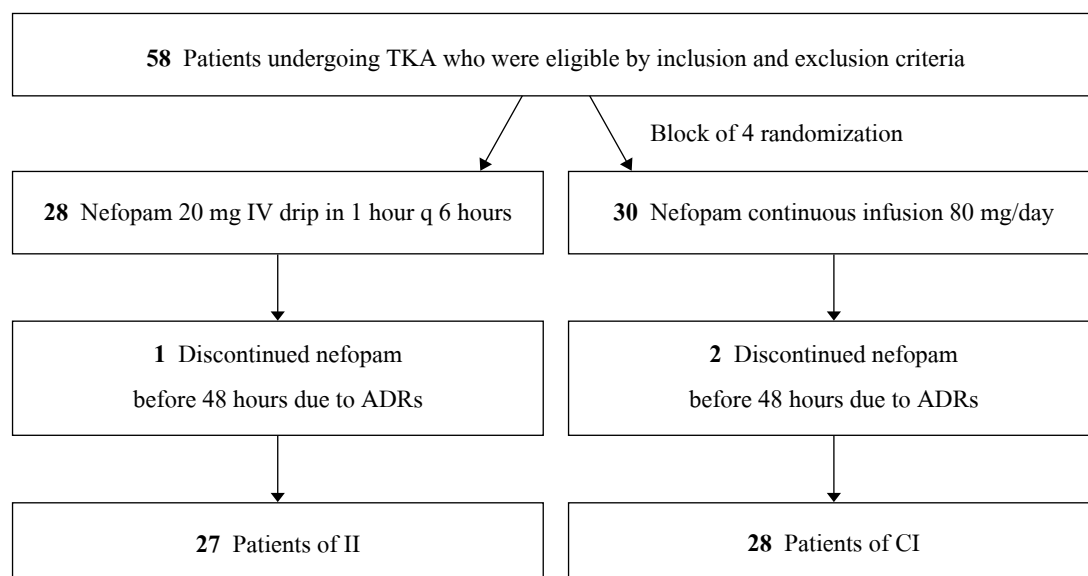
Pain scores were significantly different at 4 hours, 24 hours, and 36 hours. At 4 hours, the II group had significantly lower pain scores than the CI group (median [range], 0 [0-4] in the II group and 0 [0-8] in the CI group; $P = .008$). However, at 24 hours and 36 hours, which were the pain scores before the subsequent dose in the II group, the CI group had significantly lower pain scores than the II group; median (range), 0 (0-5) in the CI group vs 2 (0-9) in the II group at 24 hours ($P = .020$), and 0 (0-4) in the CI group vs 2 (0-8) in the II group at 36 hours ($P = .014$).

At other time points, there was no significant difference in pain scores (Figure 2).

ADRs

The adverse events were comparable in both groups (Table 3). ADRs found in this study were nausea, vomiting, dizziness, and agitation. Most ADRs were self-limiting or relieved after receiving treatment medication (IV ondansetron, IV dimenhydrinate). Three patients had to discontinue nefopam before the 48-hour study period. One patient in the II group still had nausea after receiving ondansetron. In the CI group, one patient had aggravated nausea and vomiting and developed hyponatremia, hypokalemia, and hypomagnesemia. The patient was unconscious and was taken to an intensive care unit for immediate care and monitoring. The other patient had nausea, vomiting, dizziness, and agitation and did not recover after receiving ondansetron and dimenhydrinate.

Figure 1. Study Flow Chart



Abbreviations: ADRs, adverse drug reactions; CI, continuous infusion; II, intermittent infusion; IV, intravenous; q, every; TKA, total knee arthroplasty.



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Table 1. Patients Characteristics

Characteristic	Nefopam Regimen		P Value [*]
	II 20 mg IV q 6 h (n = 28)	CI 80 mg/day (n = 30)	
Age, mean (SD), y	72 (7.1)	69.5 (7.0)	.168 ^a
Sex, No (%)			
Male	2 (7.1)	3 (10.0)	1.000 ^b
Female	26 (92.9)	27 (90.0)	
Weight mean (SD), kg	67.2 (10.7)	64.5 (9.6)	.316 ^a
Height, median (range), cm	155 (145 - 174)	151.5 (145 - 173)	.204 ^c
Underlying disease			
Hypertension	20 (71.4)	20 (66.7)	.780 ^d
DM type 2	9 (32.1)	8 (26.7)	.775 ^d

Abbreviations: CI, continuous infusion; DM, diabetes mellitus; II, intermittent infusion; IV, intravenous; q, every.

^{*} $P \leq .05$ was considered statistically significant.

^a Data analyses performed with unpaired *t* test.

^b Data analyses performed with Fisher exact test.

^c Data analyses performed with Mann-Whitney *U* test.

^d Data analyses performed with chi-square test.

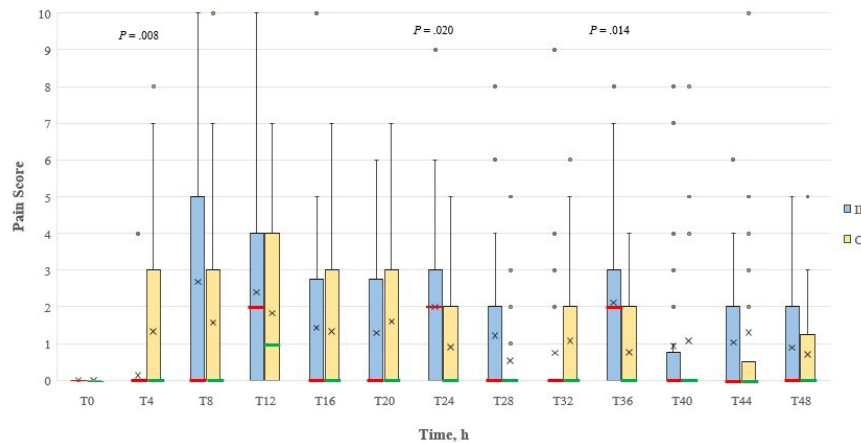
Table 2. Cumulative Morphine Consumption After the First Dose of Nefopam

Time After the First Dose of Nefopam, h	Morphine Consumption, Median (range), mg		
	Nefopam Regimen		
	II 20 mg IV q 6 h	CI 80 mg/day	P Value [*]
	(n = 28)	(n = 30)	
0 - 12	2 (0 - 9)	2.5 (0 - 11)	.629
0 - 24	3 (0 - 12)	4 (0 - 12)	.666
0 - 36	3 (0 - 14)	6 (0 - 17)	.491
0 - 48	4 (0 - 16)	6 (0 - 18)	.579

Abbreviations: CI, continuous infusion; II, intermittent infusion; IV, intravenous; q, every.

^{*} Data analyses performed with Mann-Whitney *U* test, with a significance threshold of $P \leq .05$.

Figure 2. The Box and Whisker Plots Compare the Pain Score Data Every 4 Hours After Administering the First Nefopam (T0) Dose Between the II and CI Groups



The bars represent Q1 to Q3, the upper bars indicate the upper whisker ($Q3 + 1.5[IQR]$), the dots represent outliers, — represent medians of II, — represent medians of CI, and × represents the mean pain scores of both the II and CI groups. Abbreviations: CI, continuous infusion; II, intermittent infusion; IQR, interquartile range; Q, quartile.

Table 3. ADRs in 48-Hour Study Period Between the II And the CI Group

ADRs	Experienced ADRs, No. (%)		P Value*
	Nefopam Regimen		
	II 20 mg IV q 6 h	CI 80 mg/day	
	(n = 28)	(n = 30)	
Nausea	17 (60.7)	15 (50)	.441
Vomiting	13 (46.4)	12 (40)	.791
Dizziness	4 (14.3)	4 (13.3)	1.000
Agitation	0	1 (3.3)	1.000

Abbreviations: ADRs, adverse drug reactions; CI, continuous infusion; II, intermittent infusion; IV, intravenous; q, every.

* Data analyses performed with Mann-Whitney *U* test, with a significance threshold of $P \leq .05$.

Discussion

Since no prior studies had directly compared the morphine-sparing effects between II and CI of nefopam, the minimum clinically important difference (MCID) in morphine reduction between these regimens was unknown. This study utilized distribution-based methods to calculate

the effect size from morphine consumption data of II and CI studies (mean [SD], 21 [13.5]¹¹ and 39 [28]¹³ mg, respectively), yielding an effect size of 0.8. However, our study found no significant difference in cumulative morphine consumption between the 2 methods. For future studies, a larger sample size may be necessary to detect smaller differences between these 2 regimens.



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Significant differences in pain scores were observed at 4, 24, and 36 hours between the II and CI groups. Specifically, at the 4-hour mark, the II group reported significantly lower pain scores compared to the CI group. This can be attributed to the pharmacokinetics of IV administration, where the II regimen reaches its maximum concentration (T_{max}) more rapidly than the CI regimen.¹⁵ Consequently, the II group experienced lower pain scores at the 4-hour mark. Furthermore, when comparing the pain scores at trough concentration (before the subsequent dose), the CI group demonstrated significantly lower pain scores at 24 and 36 hours. This observation can be explained by the pharmacokinetics of nefopam, which has an elimination half-life of about 4 hours.¹⁸ By the 24- and 36-hour marks, nefopam had achieved a steady state. Therefore, the CI group likely sustained more consistent plasma levels of nefopam within the therapeutic window.

ADRs identified in this study included nausea, vomiting, dizziness, and agitation, which are common to both opioids and nefopam.^{8, 10, 19} Therefore, these side effects probably likely resulted from the concurrent use of these medications. Notably, 3 participants could not complete the study due to these adverse reactions. Variations in response to these medications may be attributed to CYP2D6 polymorphism. Previous studies by Dagostino et al²⁰ and Rattana-arpa et al²¹ have demonstrated that individuals who are ultrarapid metabolizers of CYP2D6 exhibit enhanced conversion of codeine to morphine, its active form. This increased conversion rate could lead to a higher incidence of codeine-related side effects in these patients.

This study was limited by the absence of therapeutic drug monitoring and direct comparison of plasma levels between the II and CI regimens, leaving the detailed pharmacokinetics and their impact on efficacy unexplored. The lack of blinding among participants might have biased reported pain scores. Additionally, distinguishing specific adverse effects such as nausea, vomiting, and dizziness as solely due to nefopam was challenging due to concurrent

opioid use, which shares similar side effects. This study did not employ repeated measure analysis, potentially limiting conclusive insights from time-related pain scores. Lastly, the applicability of the results is primarily relevant to patients undergoing primary TKA with a comparable multimodal analgesic regimen.

Conclusions

This study found no significant difference in the morphine-sparing effect and incidence of ADRs during the 48-hour follow-up period between intermittent and continuous administration of nefopam as part of multimodal analgesia in patients after total knee arthroplasty.

Article Information

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Ethics Approval

This study was conducted in Ramathibodi Hospital in Thailand, following local ethics committee approval, Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA 2021/167 on March 8, 2021). Before initiating the study, researchers must obtain written informed consent from each participant, duly signed to document their agreement to participate. This study has been registered with the Thai Clinical Trials Registry (TCTR) under the registration number TCTR202103160010 on March 16, 2021.

Financial Support

No financial support was provided for the study.

Conflict of Interest

The authors declare no conflict of interest in this study.



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