Clinical Trial/Experimental Study

Medicine

OPEN

Postoperative analgesia of intraoperative nefopam in patients undergoing anterior cervical spine surgery

A prospective randomized controlled trial

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Abstract

Background: Nefopam is a non-opioid, non-nonsteroidal anti-imflammatory drug, analgesic drug that inhibits the reuptake of serotonin, norepinephrine, and dopamine. It is widely used as an adjuvant for pain. This study investigated whether the intraoperative, intravenous infusion of nefopam (20 mg) reduces postoperative morphine consumption, pain scores, and alleviates neuropathic pain in patients undergoing cervical spine surgery.

Methods: A prospective, paralleled design, randomized study was conducted on 50 patients (aged 18–75 years) in a university-based hospital. The patients were assigned to an intervention or a control group (25 patients in each). The intervention group received a 1-hour infusion of nefopam (20 mg) before the end of surgery. The control group received normal saline (NSS). The outcome measures were morphine consumption during the first 24 postoperative hours, numerical rating scale (NRS) pain scores, and scores for the Thai version of the Neuropathic Pain Symptom Inventory (NPSI-T) in patients with neuropathic pain and adverse drug reactions. The NPSI-T scores were assessed on the preoperative day, postoperative day 1, 3, 15, and 30. The outcome assessors were blinded to group allocation.

Results: Fifty patients were analyzed. During the first 24 postoperative hours, morphine consumption was 8 mg (nefopam) and 12 mg (NSS; $P = .130$). The intervention and control groups demonstrated no significant differences in the median NRS scores or total NPSI-T scores or adverse drug reactions.

Conclusions: A single, intraoperative infusion of 20 mg of nefopam did not significantly reduce postoperative (24 hours) morphine consumption in patients undergoing anterior cervical spine surgery.

Abbreviations: NPSI-T = Thai version of the Neuropathic Pain Symptom Inventory, NRS = numerical rating scale, NSS = normal saline.

Keywords: adverse drug reactions, analgesic drug, morphine, nefopam, neuropathic pain, pain, spine

1. Introduction

Cervical spondylosis myelopathy is a common cause of disabilities in many adult patients.[1] Patients may present with neck pain, paresthesia, or muscle weakness corresponding to the involved nerve root or the spinal cord. The primary treatment of myelopathy is surgery, which has 2 approaches: anterior and posterior. The typical techniques of the anterior approach include anterior cervical discectomy and fusion (ACDF), anterior cervical corpectomy and fusion, and total disc replacement. Postoperative pain is usually at a moderate level, but it may be inadequately treated due to concerns about respiratory depression from opioid analgesics. Some patients may also have neuropathic pain symptoms that are not usually diagnosed or whose severity is not assessed.

Nefopam, a benzoxazocine derivative, is a non-opioid, non-nonsteroidal anti-inflammatory drug analgesic. The mechanisms of its analgesic effects are unclear. However, current knowledge indicates that nefopam inhibits the reuptake of serotonin, norepinephrine, and dopamine. As its mechanism is similar to those of some antidepressants and anticonvulsants, nefopam is suitable for the treatment of both nociceptive pain

The authors have no conflicts of interest to disclose.

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

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This research project was supported by the Faculty of Medicine, Siriraj Hospital, Mahidol University (grant [IO] R016231030).

How to cite this article: Raksakietisak M, Rushatamukayanunt P, Wilaiwan K, Homprasert C, Nitising A, Sawasdiwipachai P, Pantubtim C. Postoperative analgesia of intraoperative nefopam in patients undergoing anterior cervical spine surgery: A prospective randomized controlled trial. Medicine 2022;101:43(e31296).

Received: 28 May 2022 / Received in final form: 19 September 2022 / Accepted: 20 September 2022

http://dx.doi.org/10.1097/MD.0000000000031296

and neuropathic pain.[2,3] Researches revealed that the drug is a centrally acting, non-opioid analgesic; is a N-methyl-D-aspartate (NMDA) receptor antagonist; and inhibits voltage-sensitive sodium channels.[4,5] It has been demonstrated antiallodynic effects of nefopam in a neuropathic pain model, and the ATP-sensitive potassium channel may be involved.[6] In a rat model study of pain induced by formalin, intrathecal nefopam significantly increased serotonin and norepinephrine levels, and it reduced the release of glutamate in the spinal cord.[7]

The known adverse effects of nefopam are nausea, vomiting, sweating, dizziness, drowsiness, and tachycardia.[2] It should therefore be administered with slowly intravenous infusion as a single, 20-mg dose, followed by a continuous infusion of 60 to 120 mg/day.[2]

This study was performed to investigate whether the intraoperative, intravenous infusion of 20 mg of nefopam near the end of an operation would reduce postoperative morphine consumption, postoperative pain, and neuropathic pain.

Neuropathic pain in this work was assessed by using the Thai version of the Neuropathic Pain Symptom Inventory (NPSI-T) score. This tool utilizes a self-administered questionnaire to evaluate the positive symptoms of neuropathic pain. Validated versions of the questionnaire exist in many languages, such as German, Italian, and Thai. The psychometric properties of the instrument suggest that it can be used to characterize subgroups of neuropathic pain patients and to evaluate their response to pain treatment.[8] The numerical scales range from 0 to 10 for each item in the questionnaire and the total score is given by the sum of the 10 descriptors; it ranges from 0 to 100.[8,9]

2. Methods

This study was designed as a single-center, prospective, randomized trial with 2 parallel treatment groups receiving either nefopam or normal saline. It was conducted at a university-based hospital in Bangkok, Thailand, between May 2019 and March 2021. Before commencement of this research, its protocol was approved by the Institutional Review Board (Si 204/2019), and the project was registered at Clinical Trials.gov (NCT03955705). Fifty patients were enrolled and had given informed consent. All were undergoing elective anterior cervical spine surgery, such as ACDF or anterior cervical corpectomy and fusion. The enrollments were undertaken in the orthopedic and neurosurgery patient wards on the day before surgery. The participants were allocated to 2 groups using computer-generated randomization in blocks of 4. The sequence numbers and groups were placed inside concealed envelopes; these were opened once written informed consent was obtained. The researchers enrolled the participants, but they did not take part in patient care.

The other inclusion criteria were a patient age of 18 to 75 years, an American Society of Anesthesiologists physical status of I to III, a body weight over 50 kg, and a body mass index (BMI) below 30 kg/m^2. The exclusion criteria were an allergy to, or contraindications for, nefopam (such as epilepsy)[3]; coronary artery disease; a history of myocardial infarction; angle-closure glaucoma; any psychiatric disorder; preoperative use of a monoamine oxidase inhibitor; a creatinine clearance below 30 mL/min; pregnancy; and breastfeeding. In addition, patients who could not read or comprehend the questions in the NPSI-T were excluded.

Before admission, all participants had laboratory investigations as per hospital protocol. One day before their surgery, potentially eligible patients were assessed for inclusion in the study. Upon giving their consent to participate, the enrolled patients underwent neuropathic pain screening with the Thai version of the diagnostic neuropathic pain questionnaire (Douleur Neuropathique 4).[10] If a patient's score exceeded 4, the severity of the neuropathic pain was assessed using NPSI-T.

Intraoperatively, standard monitoring with or without invasive arterial blood pressure monitoring was performed for all patients. General anesthesia was induced with propofol (1.5–2 mg/kg) and fentanyl (1–2 mcg/kg). Cis-atracurium (0.15 mg/kg) was also administered to facilitate endotracheal intubation. The anesthesia was maintained with desflurane (0.5–1.5 minimal alveolar concentration); a continuous intravenous infusion of cis-atracurium (0.06–0.1 mg/kg/hr); and intermittent doses of fentanyl (0.5–1 mcg/kg). The cis-atracurium was discontinued half an hour before the end of the operation.

To prevent postoperative nausea and vomiting, a prophylaxis regimen was administered. It comprised of dexamethasone (10 mg after induction of anesthesia) and ondansetron (8 mg before the finish of the operation).

The researchers managed the study drug, nefopam (Acupan®, DELPHARM TOURS, France) or normal saline (NSS). Depending on whether a patient had been randomized to the intervention or the control group, the coordinator prepared either 20 mg of nefopam in 20 mL of NSS, or just 20 mL of NSS. These preparations were contained in identical 20 mL syringes. The on-site anesthesiologist, who was blinded to the treatment, commenced the administration of the drug allocated to a patient (nefopam or NSS) 1 hour before the cervical spine surgery finished. The infusion of the nefopam or NSS lasted 1 hour.

At the end of the operation, the neuromuscular blockade was reversed with glycopyrrolate (0.4 mg) and neostigmine (2.5 mg). The patients were extubated once they were fully awake and met the criteria for extubation. They were subsequently transferred to the postanesthesia care unit. All participants were given an intravenous, patient-controlled analgesia (IV PCA) device. The analgesia was commenced in the postanesthesia care unit without a loading dose. The device was programmed with no basal infusion rate, a patient-controlled dose of 1 mg of morphine, a lockout interval of 10 minutes, and a 4-hour limit of 10 mg of morphine. The participants also received paracetamol (1000 mg orally every 6 hours, for 24 hours).

The 24-hour postoperative morphine consumption was recorded by using intravenous patient-controlled analgesia (IV PCA) device. Pain intensity was measured by the numerical rating scale (NRS) at 0 hour in the postanesthesia care unit, and later in the patient's ward at 4, 8, 12, 16, 20, 24, 48, and 72 hours postoperatively. Furthermore, with the patients whose preoperative evaluations indicated the presence of preexisting neuropathic pain, their NPSI-T subscale scores and total intensity scores were assessed on preoperative period, postoperative day 1, 3, 15, and 30. The 5 subscale dimensions comprised "burning (superficial) spontaneous pain," "pressing (deep) spontaneous pain," "evoked pain," "paresthesia/dysesthesia," and "pins and needles/tingling." Adverse reactions during the intraoperative period were also recorded. The researcher who determined the NRS and NPSI-T scores was blinded to the group allocations.

2.1. Statistical analysis

A previous study on patients who underwent ACDF surgery reported a mean morphine consumption of 4 mg with standard deviation (SD) of 2 during the initial 24-hour postoperative period.[11] We expected that the nefopam intervention would result in a 50% reduction in morphine consumption, in other words, 2 mg instead of 4 mg. Calculation of the sample size was carried out with the n4Studies program. Using a type I error of 5% and a type II error of 10%, the sample size of each group was determined to be 22 participants. The authors enrolled 25 patients each in the intervention and control groups to compensate for possible participant drop-out during the trial period.

Continuous variables with normal and abnormal distribution were compared with Student's t test or Mann–Whitney U test. The results are presented as mean ± standard

deviation or median and interquartile range, as appropriate. Categorical variables were compared using Fisher's exact test or the chi-squared test, and they are reported as number and percentage. A probability (P) value of <.05 was considered statistically significant. We used the statistical software package PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL).

3. Results

Of 63 potentially eligible patients who were screened, 50 were enrolled and included in the final analysis. No patient dropped out during the course of the study (Fig. 1). The patients' demographic characteristics were similar, except for a significant but small difference in BMI (25.0 ± 3.2 vs 22.8 ± 3.4, P = .023 [Table 1]).

The median, 24-hour, morphine consumptions of the intervention and control groups were 8 mg and 12 mg, respectively (P = .130; Fig. 2). As to the NRS results, there was no statistical difference in the median postoperative scores of the 2 groups (P = .465). Moreover, the pain intensity tended to decrease after the first 4 postoperative hours in both groups, generally declining steadily during the remainder of the first 24 postoperative hours (Fig. 3).

The median total NPSI-T scores of the 2 groups were not significantly different (P = .945). The medians of the total scores tended to decline over time. As to the median scores for the 5 NPSI-T subscale dimensions, there were no statistical differences between the corresponding median scores of the intervention and control groups (Table 2). The NPSI-T scores of both groups were quite low, and they had fallen to 0 by postoperative day 15 in all patients.

The most common adverse drug reaction in the intervention group was hypertension. However, there was no difference between the groups (Table 3). The nefopam group did not report any postoperative complications, like nausea, vomiting, sweating, or confusion.

All of the operations were uneventful, with no major surgical complications. All patients were safely discharged.

4. Discussion

In this randomized controlled study, 20 mg of nefopam was administered to the patients in the intervention group throughout the 1-hour period before the end of their cervical spine surgery. Postoperatively, however, this intraoperative drug administration did not result in any statistical differences in the initial 24-hour morphine consumption levels or the pain scores. The median effective dose of nefopam in minor surgery was previously found to be 18 mg,[12] so we chose a single dose of 20 mg as a preventive analgesia after anterior cervical spine surgery. Cervical spine surgery is considered to involve mild to moderate pain levels,[1,11] we considered a single dose of 20 mg of nefopam should be adequate for pain prevention.

From the demographic results, the nefopam group had a higher BMI with statistical significance but not clinical significance. We considered 20 mg of nefopam might be inadequate for obese patients, so we excluded obese patients (BMI > 30 kg/m^2) from this study.

In major surgery, the dose of nefopam used to reduce morphine consumption during the first 24 postoperative hours has been reported to be as high as 120 mg.[13–16] For several decades, nefopam has been widely used for acute postoperative pain in several settings[13] such as endoscopic lumbar discectomy,[17] breast cancer surgery,[18] and laparoscopic gastrectomy.[19] A meta-analysis[20] which included 4 randomized controlled trials on intravenous nefopam-reported that the drug significantly reduced postoperative pain scores, opioid requirements, and opioid-related adverse effects after laparoscopic cholecystectomy.

From our previous study, the most severe pain in ACDF surgery was experienced 4 to 8 hours after the operation,[12] and a single dose of nefopam should be adequate to cover the early postoperative-pain. Although the 24 hours. morphine consumption in this study was less in the nefopam group, the result did not reach statistical significance. Our results were in concordance with those of another recent investigation[21] on the use of nefopam in patients undergoing lumbosacral spine surgery. That study chose a single

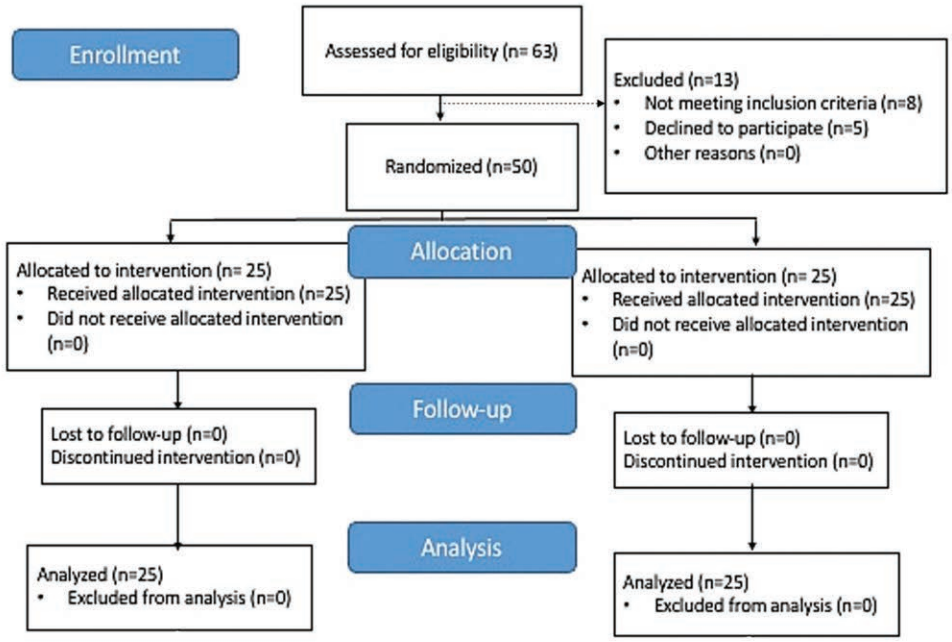

Figure 1. Consort flow diagram.

Table 1

Baseline characteristics of the study participants.

Patient	Intervention group (nefopam) (n = 25)	Control group (normal saline) (n = 25)	*P* value
Male/female	14/11	14/11	1.000
Age	57 ± 11	55 ± 14	.524
BMI (kg/m^2)	25.0 ± 3.2	22.8 ± 3.4	.023*
ASA			.291
1	4 (16%)	9 (36%)	
2	16 (64%)	13 (52%)	
3	5 (20%)	3 (12%)	
Number of spines involved in surgery			.347
1–2 levels	22 (88%)	20 (80%)	
≥3 levels	3 (12%)	5 (20%)	
Symptoms			
Paresthesia	19 (76%)	20 (80%)	.733
Weakness	16 (64%)	12 (48%)	.254
Pain	10 (40%)	12 (48%)	.569
Neuropathic pain			
DN4 ≥ 4 (eligible for assessed NPSI-T)	8 (32%)	12 (48%)	.248
NPSI-T total scores	15 (13.25, 21.75)	17.5 (11, 25.5)	.910
NPSI-T subscale scores			
BSSP	0 (0,0)	0 (0, 4.5)	.521
PDSP	0.5 (0, 2.75)	1 (0, 4.12)	.792
EP	1.25 (0.12, 3.12)	2 (1.5, 3.75)	.305
P/D	0 (0,0)	0 (0, 1.83)	.135
PN/T	4.25 (3.5, 5)	3 (2.5, 3.87)	.181
Length of hospital stay	5 (4, 6)	4 (4, 5)	.484

Data presented as number (%) and as mean ± standard deviation (SD), median (interquartile ranges), as appropriate. NPSI-T is divided into 5 subscales. Each subscale ranges from 0 to 10, and the total NPSI-T ranges from 0 to 100 (score from the questionnaires, not from the summation of each subscale).

DN4 = douleur neuropathique, NPSI-T = Thai version of Neuropathic Pain Symptom Inventory, BSSP = burning (superficial) spontaneous pain, PDSP = pressing (deep) spontaneous pain, EP = evoked pain, P/D = paresthesia/dysesthesia, PN/T = pins and needles/tingling.

*$P < .05$ considered statistically significant.

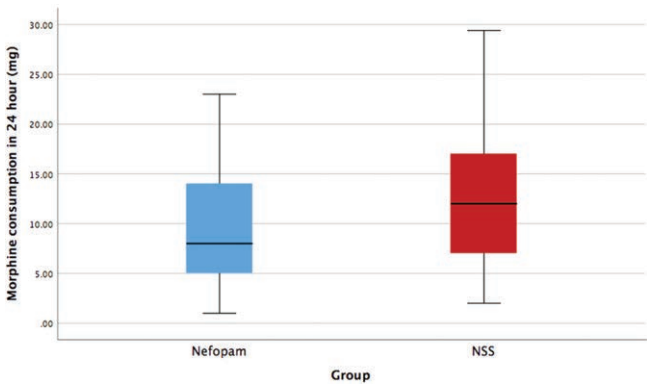

Figure 2. Comparison of the median, 24 hr, morphine consumptions of the intervention (nefopam) and control (normal saline) groups.

dose of 30 mg of nefopam, which was given either before the surgical incision or before the end of the operation. The trial results did not demonstrate any analgesic efficacy on the 24-hour morphine consumption. A single dose of nefopam might be insufficient to control moderate pain in an ACDF or lumbosacral spine operation. In a previous study,[22] an animal model showed a synergistic antinociceptive interaction between low doses of nefopam and paracetamol to treatment of postoperative hypersensitivity to peripheral stimuli. In both groups, all patients received oral paracetamol which may cover mild to moderate postoperative pain after anterior cervical surgery.

In previous studies,[2,14–16] hypertension and tachycardia were found to be the most common, adverse, intraoperative drug reactions in intervention and control groups. However, we observed that hypertension, hypotension, and bradycardia were the predominant reactions during intraoperative drug infusion. As those 3 adverse events were found in both the intervention and the control groups. The bradycardia and hypotension may be related to vagal stimulation during the surgery.

In addition, the intervention group did not experience any postoperative complications or adverse reactions related to the administration of the nefopam. This contrasted with the findings of other studies that had reported that nefopam could cause tachycardia, hypertension, dizziness, and sweating[7,14] Our regimen – a 1-hour infusion of 20 mg of nefopam, commencing an hour before the end of the operation – could avoid a high peak plasma concentration, which may be associated with the adverse reactions of nefopam.

Several studies[23–25] discovered that co-administering nefopam with several analgesics via patient-controlled analgesia (PCA) for postoperative pain management may allow for opioid dose reduction, lowering the risk of opioid-related adverse effects.

Several limitations must be noted. Although we excluded patients with a BMI > 30 kg/m^2, the mean BMI of the intervention group was higher than that of the control group. This might have affected the study results. Moreover, some patients took preoperative gabapentinoids (pregabalin or gabapentin) and pain medications (opioid and non-opioid drugs). As those drugs were neither controlled nor excluded, their usage might have affected the results. However, because blinded randomization was employed, the patients on chronic-pain medications were equally distributed between the intervention and control groups (Table 1). Finally, patients with underlying diseases (like coronary artery disease) and the elderly were not enrolled. This is because we were concerned about the side effects of nefopam in such patients. Future research might not only change the drug regimen to a 24-hour nefopam infusion, but also utilize a larger sample size for the neuropathic pain analyses.

To our knowledge, this is the first study to investigate whether a single dose of nefopam can reduce the postoperative morphine consumption of patients undergoing anterior cervical spine surgery.

5. Conclusions

In conclusion, a single, intraoperative, intravenous infusion of 20 mg of nefopam did not significantly reduce morphine consumption during the first 24-hour postoperative period in patients undergoing anterior cervical spine surgery. An hour infusion of 20 mg of nefopam showed no significant adverse events in these patients.

Acknowledgments

The authors are grateful to Mrs. Orawan Supapeung for the statistical analyses; and Miss Nichapat Thongkaew, Miss Chusana Rungjindamai, and Miss Nattaya Bunwatsana for coordinating the study. The authors also thank Mr. David Park for his careful proofreading and professional English editing of this manuscript.

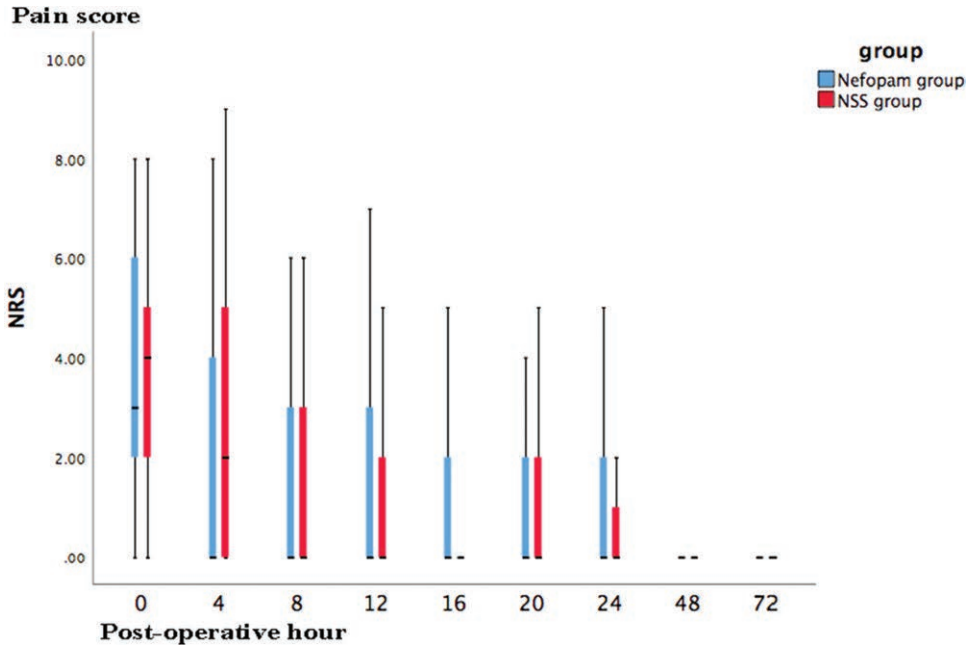

Figure 3. Comparison of the median scores for the numeric rating scale of postoperative pain of the intervention (nefopam) and control (normal saline) groups during the study period. NRS = numeric rating scale.

Table 2

Subscale and total scores for Thai version of Neuropathic Pain Symptom Inventory of (NPSI-T) during the study period.

Scores	NFP-D1	NSS-D1	NFP-D3	NSS-D3	NFP-D15	NSS-D15	NFP-D30	NSS-D30
BSSP	0 (0, 0)	0 (0, 0.7)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
PDSP	0 (0, 0.7)	1 (0, 2.8)	0 (0, 0.3)	0.2 (0, 1.6)	0 (0, 0)	0 (0, 0.3)	0 (0, 0)	0 (0, 0)
EP	0 (0, 0.3)	0.2 (0, 1.5)	0 (0, 0.3)	0 (0, 0.5)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
P/D	0 (0, 0)	0.6 (0, 1.2)	0 (0, 0)	0.5 (0, 0.9)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
PN/T	1.2 (0, 2.3)	1 (0.1, 2.3)	0 (0, 0.5)	0.5 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Total NPSI-T	4.3 (2.2, 11)	7 (4.2, 19.2)	1 (0, 2.5)	3.1 (1.1, 10.7)	0 (0, 0.9)	0 (0, 2.2)	0 (0, 0)	0 (0, 0.7)

Data presented as median (interquartile ranges) due to abnormal distribution. NPSI-T is divided into 5 subscales. Each subscale ranges from 0 to 10, and the total NPSI-T ranges from 0 to 100 (score from the questionnaires, not from the summation of each subscale).

BSSP = burning (superficial) spontaneous pain, D1 = postoperative day 1, D3 = postoperative day 3, D15 = postoperative day 15, D30 = postoperative day 30, EP = evoked pain, NFP = nefopam, NPSI-T = Thai version of Neuropathic Pain Symptom Inventory, NSS = normal saline, P/D = paresthesia/dysesthesia, PDSP = pressing (deep) spontaneous pain, PN/T = pins and needles/tingling.

Table 3

Adverse events during study-drug infusion.

	Intervention group (nefopam) (n = 25)	Control group (normal saline) (n = 25)	*P* value
Hypertension (SBP > 140 mm Hg)	8 (32%)	5 (20%)	.333
Hypotension (SBP < 90 mm Hg)	4 (16%)	4 (16%)	1.000
Bradycardia (HR < 60/min)	4 (16%)	2 (8%)	.669
Tachycardia (HR > 100/min)	2 (8%)	2 (8%)	1.000

Data presented as number (%).

HR = heart rate, SBP = systolic blood pressure.

Author contributions

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Supervision: Manee Raksakietisak.

Writing – original draft: Manee Raksakietisak, Pranee Rushatamukayanunt, Prasert Sawasdiwipachai.

Writing – review & editing: Manee Raksakietisak, Pranee Rushatamukayanunt.

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