Pain Physician 2022; 25:491-500 • ISSN 1533-3159

Randomized Controlled Trial

Effect of Continuous Infusion of Intravenous Nefopam on Postoperative Opioid Consumption After Video-assisted Thoracic Surgery: A Double-blind Randomized Controlled Trial

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Disclaimer: Sponsorship for this study was funded by Pharmbio Korea Co., Ltd., Korea.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-06-2022
Revised manuscript received: 03-27-2022
Accepted for publication: 05-11-2022

Background: Although nefopam has been reported to have opioid-sparing and analgesic effects in postsurgical patients, its effectiveness in video-assisted thoracoscopic surgery (VATS) is unknown.

Objectives: This study aimed to investigate the opioid-sparing and analgesic effects of perioperative nefopam infusion for lung resection.

Study Design: Double-blinded randomized controlled trial.

Setting: Operating room, postoperative recovery room, and ward at a single tertiary university hospital.

Methods: Ninety patients scheduled for elective VATS for lung resection were randomized to either the nefopam (group N) or control group (group C). Group N received 20 mg nefopam over 30 minutes immediately after the induction of anesthesia. Nefopam was administered continuously for 24 hours postoperative, using a dual-channel elastomeric infusion pump combined with fentanyl-based intravenous patient-controlled analgesia. Group C received the same volume of normal saline as nefopam solution administered in the same manner. The primary outcome measure was fentanyl consumption for the first postoperative 24 hours. The secondary outcome measures were the cumulative fentanyl consumption during the first postoperative 48 hours, pain intensity at rest and during coughing evaluated using an 11-point numeric rating scale, quality of recovery at postoperative time points 24 hours and 48 hours, and the occurrence of analgesic-related side effects during the first postoperative 24 hours and postoperative 24 to 48 hour period. Variables related to chronic postsurgical pain (CPSP) were also investigated by telephone interviews with patients at 3 months postoperative. This prospective randomized trial was approved by the appropriate institutional review board and was registered in the ClinicalTrials.gov registry.

Results: A total of 83 patients were enrolled. Group N showed significantly lower fentanyl consumption during the first postoperative 24 hours and 48 hours (24 hours: median difference: -270 μg [95%CI, -400 to -150 μg], $P < 0.001$); 48 hours: median difference: -365 μg [95% CI: -610 to -140 μg], $P < 0.001$). Group N also showed a significantly lower pain score during coughing at 24 hours postoperative (median difference, -1 [corrected 95% CI: -2.5 to 0], adjusted $P = 0.040$). However, there were no significant between-group differences in the postoperative quality of recovery, occurrence of analgesic-related side effects, length of hospital stay, and occurrence of CPSP.

Limitations: Despite the significant opioid-sparing effect of perioperative nefopam infusion, it would have been difficult to observe significant improvements in other postoperative outcomes owing to the modest sample size.

Conclusion: Perioperative nefopam infusion using a dual-channel elastomeric infusion pump has a significant opioid-sparing effect in patients undergoing VATS for lung resection. Therefore, it could be a feasible option for multimodal analgesia in these patients.

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Key words: Analgesia, analgesics, opioid, lung neoplasms, nefopam, perioperative care, postoperative pain, thoracic surgery, video-assisted

Pain Physician 2022: 25:491-500

Compared with the thoracotomy approach, video-assisted thoracoscopic surgery (VATS) enables faster postoperative recovery by reducing surgical stress (1,2). However, postoperative pain remains an important complication in patients undergoing VATS for lung resection (3). Postoperative pain could be associated with an increase in patient dissatisfaction, postoperative complications, and medical costs (4-6). Additionally, uncontrolled acute postoperative pain can lead to chronic postoperative pain (CPSP) and chronic opioid use, which can lead to reduced postoperative quality of life (7,8).

Nefopam is considered as an option for multimodal analgesia owing to its opioid-sparing effect, with a different analgesic mechanism compared with other analgesics (9,10). However, there have been few studies on its effectiveness in patients undergoing surgery who are under multimodal analgesia (11), which has become the standard of care for patients undergoing surgery.

A recent study evaluated the opioid-sparing and pain relief effects of nonopioid analgesic combinations, including nefopam; however, this study did not have sufficient power to evaluate its primary outcome due to an unplanned interruption (12). Additionally, considering the high proportion of patients experiencing neuropathic pain after thoracic surgery (13), nefopam, which has been reported to be effective in neuropathic pain (10,14,15), could be more beneficial than other nonopioid analgesics for pain control after thoracic surgery. However, evidence on the opioid-sparing and pain relief effects of nefopam in patients undergoing thoracic surgery is rare.

Therefore, this study aimed to evaluate the benefits of perioperative nefopam infusion on opioid consumption and pain relief in patients undergoing VATS for lung resection. We hypothesized that perioperative nefopam infusion would reduce postoperative opioid consumption and pain intensity in these patients. In addition, the effects of nefopam on the occurrence of analgesic-related side effects, quality of postoperative recovery, and occurrence of CPSP were also investigated.

Methods

Study Design and Patients

This prospective randomized trial was approved by the appropriate institutional review board and was registered in the ClinicalTrials.gov registry (NCT04450355, date of registration: June 24, 2020). The study design and reporting of findings followed the Consolidated Standards of Reporting Trials recommendations (16). All patients provided written informed consent before enrollment.

Adult patients aged 19 to 70 years who were scheduled for elective VATS for lung resection at Seoul National University Hospital, South Korea from July 2020 through August 2021 were eligible. The exclusion criteria were as follows: 1) American Society of Anesthesiologists (ASA) physical status III or higher; 2) refusal of intravenous patient-controlled analgesia (IV-PCA); 3) chronic pain for more than 3 months; 4) pregnancy or lactation; 5) allergy to the study anesthetic or analgesic medications; 6) medical or psychological diseases that could affect treatment response; 7) contraindications to nefopam (myocardial infarction, a history of convulsive disorders, taking monoamine oxidase inhibitors); 8) inability to understand the study protocol and provide informed consent; and 9) planned postoperative analgesia other than the analgesia included in the study protocol.

The dropout criteria were withdrawal of consent, surgery cancellation, unexpected thoracotomy conversion, and mechanical ventilation for > 2 hours after surgery. The participating patients were informed on the use of IV-PCA and the method of pain assessment before surgery. They were also asked to answer the Korean version of the Quality of Recovery-15 (QoR-15K) questionnaire (17).

The baseline characteristics of the patients were recorded, including age, gender, height, weight, body mass index, ASA physical status, preoperative QoR-15K score, type of surgery, duration of surgery, and intraoperative remifentanil consumption.

Randomization and Blinding

After enrollment, the patients were randomly assigned to the nefopam (Group N) or the control group (Group C) with block randomization (block size: 4 and 6) in a 1:1 allocation ratio using the R software (Version 3.5.1, R Foundation for Statistical Computing). Randomization was performed by an anesthesiologist blinded to the study. A randomization list was sent to a nurse who was also not involved in the study. The

nurse prepared the IV-PCA; 20 mg nefopam with 98 mL normal saline (total 100 mL) or placebo solution (normal saline 100 mL) was planned to be administered immediately after induction.

PCA Protocol

A dual-infusion elastomeric pump with 2 balloon chambers (Bellomic Duo, Cebika, Uiwang-si) was used for IV-PCA. One channel was used for bolus function (bolus channel), while the other channel was used for continuous infusion at a constant flow rate (basal channel). The bolus channel was prepared with fentanyl 20 μg/mL with a bolus dose of one mL and a lock-out interval of 10 minutes. The basal channel was prepared at a continuous infusion rate of 2 mL/hr with 60 mg of nefopam (6 mL) in 44 mL normal saline for Group N or 50 mL normal saline alone for Group C. Given that the nefopam solution was clear and the nefopam and placebo solutions were labeled with the same name in the 2 groups, all patients and physicians who evaluated the postoperative outcomes were blinded to the group assignment.

Perioperative Management

All patients were monitored and managed similarly following institutional standard care practices. All patients received preoperative carbohydrate loading (Nucare NONPO, Daesang Co.) 2-3 hours before surgery. Without premedication, patients received total intravenous anesthesia (TIVA) with a target-controlled infusion of propofol and remifentanil and rocuronium for neuromuscular blockade intraoperatively. During induction, 0.075 mg palonosetron and 5 mg dexamethasone were administered intravenously for postoperative nausea and vomiting (PONV) prophylaxis. After anesthesia induction, 20 mg nefopam with 100 mL normal saline (Group N) or 100 mL normal saline (group C) was administered intravenously over 30 minutes. Intercostal nerve blockade using 0.25% bupivacaine was performed before the surgical incision by the attending surgeons.

VATS was performed using a 3-port technique consisting of 3 incisions (less than 5 cm) with rib sparing. Lung protective ventilation with low tidal volume (6–8 mL/kg ideal body weight for 2-lung ventilation and 4–6 mL/kg ideal body weight for one-lung ventilation) and positive end-expiratory pressure of 5–10 cm H_2O was administered. After skin closure, 30 mg ketorolac tromethamine and 50 μg fentanyl were administered intravenously and IV-PCA was connected to the patient's IV line. After reversal of neuromuscular blockade with 2–4 mg/kg sugammadex, the patients were extubated and transferred to the postanesthesia care unit (PACU).

From the PACU, the patients were permitted to use IV-PCA when they had a Numeric Rating Scale (NRS-11) pain score of ≥ 3. In addition, continuous 24-hour infusion of intravenous nefopam 60 mg (group N) or normal saline (group C) was started at a rate of 2 mL/hr via the basal channel of the IV-PCA. Patients with an NRS-11 pain score of ≥ 7 received 50 μg IV fentanyl as first-line rescue analgesia. However, those with PONV were administered 30 mg ketorolac tromethamine as an alternative rescue analgesic. Rescue antiemetics were administered upon the patient's request or upon complaint of moderate to severe PONV as follows: 1) 10 mg metoclopramide in the PACU and 2) 0.3 mg ramosetron as an initial rescue drug and 10 mg metoclopramide as a second rescue drug in the ward.

The need for rescue analgesics and antiemetics in the PACU and ward was decided by the attending physicians, who were blinded to the allocation. Water intake and ward ambulation were permitted 6 hours postoperative, and an oral extended-release tramadol 75 mg/acetaminophen 650 mg combination tablet was routinely administered at 12 hour intervals from the resumption of water intake.

Outcome Measures

The primary outcome measure was fentanyl consumption for the first postoperative 24 hours. The secondary outcome measures were cumulative fentanyl consumption during the first postoperative 48 hours; interval fentanyl consumption during 24hours–48 hours postoperative; pain intensity at rest and during coughing as evaluated using an NRS-11, postoperative QoR-15K at 24 hours and 48 hours postoperative, and the occurrence of analgesic-related side effects (nausea, vomiting, rescue antiemetic use, hydrosis, palpitation, and sedation) during the first postoperative24 hours and 24 hours–48 hours postoperative. We also investigated the rescue analgesic use during the first postoperative 24 hours and 24 hours–48 hours postoperative, length of hospital stay, and major postoperative complications (i.e., Clavien-Dindo classification grade III or higher) within 7 days postoperative (18). Additionally, we noted 1) the pain intensity at the surgical site (evaluated using NRS-11), 2) the temporal pattern of pain (persistent pain with slight fluctuations or pain attacks, and pain attacks with or without pain between them), 3) the neuropathic component (one or more of

the following symptoms: burning or tingling sensation, sharp and shocking pain, hyperalgesia, allodynia, and numbness), and 4) analgesic use was investigated by tele-interview at 3 months postoperative. Adjuvant chemotherapy within 3 months postoperative that could affect the occurrence of CPSP was also retrospectively investigated through a review of the electronic medical records (7). All outcome measures were investigated by clinicians blinded to the group allocation.

Statistical Analysis

The target sample size was calculated before the study using G*Power software Version 3.1.9 (G*Power). Based on the acute pain service database, the mean (standard deviation [SD]) postoperative fentanyl consumption during the first 24 hours in patients who underwent VATS was 450 (245) μg. Considering a 30% reduction in total fentanyl consumption for the first postoperative 24 hours in group N as clinically meaningful (effect size, 0.604), a sample size of 37 patients in each group was required to achieve 80% power to detect a statistical between-group difference on a Mann-Whitney test, with a 2-sided α of 0.05. Considering a 15% dropout rate, the target sample size was set to 45 patients per group.

All analyses were performed in accordance with the intention-to-treat principle. The normality of distribution of continuous variables was determined using the Shapiro–Wilk test. Continuous data were reported as the mean (SD) or median (interquartile range) and were compared between the 2 groups using the independent t test or Mann-Whitney U test, respectively. Meanwhile, categorical data were described as frequencies or percentages and were compared between the 2 groups using the χ^2 test or Fisher's exact test according to their expected counts. The effect sizes and their 95% confidence intervals (CIs) were also calculated. The Bonferroni correction was applied for multiple comparisons of variables other than postoperative fentanyl consumption. All statistical analyses were performed using R software Version 3.6 (The R Foundation). All statistical tests were 2-sided, and $P < 0.05$ was considered significant.

Results

Of the 115 patients assessed for eligibility, 90 patients were enrolled and randomly allocated to either Group N or Group C (Fig. 1). After recruitment, 3 patients in Group N and 4 in Group C were excluded on the day of surgery. Therefore, 83 patients were included in the analysis. Additionally, 15 patients (Group N, n = 4; Group C, n = 11) were discharged within the 48 hour postoperative period. Therefore, they were not included in the analysis of the variables investigated at 48 hours postoperative. The follow-up investigation at 3 months postoperative was conducted by tele-interview. Accordingly, except one patient who died of acute respiratory distress syndrome in Group N before investigation, all patients were included in the analysis. The baseline patient characteristics are presented in Table 1. There was no significant between-group difference in patients' characteristics, except for the duration of surgery.

Figure 2 presents a comparison of the cumulative and interval fentanyl consumption between the 2 groups. Group N showed significantly lower cumulative fentanyl consumption during the first postoperative 24 hours (median difference: -270 μg [95% CI: -400 to -150 μg], $P < 0.001$) and 48 hours (median difference: -365 μg [95% CI: -610 to -140 μg], $P < 0.001$) postoperative. Group N also showed significantly lower interval fentanyl consumption during the postoperative 24 to 48 hour period (median difference: -80 μg [95% CI: -250 to 0 μg], $P = 0.035$). Table 2 presents comparisons of the QoR-15K score, pain scores at rest and coughing, opioid- or nefopam-related symptoms, and length of hospital stay between the 2 groups. Group N showed a significantly lower pain score during coughing at 24 hours postoperative, with a median difference of -1 (corrected 95% CI: -2.5 to 0, adjusted $P = 0.040$).

There were no differences in the other postoperative outcomes (Table 3). Table 4 presents the comparison of adjuvant chemotherapy within 3 months postoperative and the CPSP-related outcomes between the 2 groups. The rates of overall CPSP, CPSP with NRS-11 $\geq$ 3, and chronic use of analgesics were 43.4%, 18.1%, and 12.0%, respectively. There were no significant between-group differences in these variables. With respect to the analgesics administered at 3 months postoperative, the most common was ibuprofen (n = 5), followed by tramadol/acetaminophen combination (n = 2), tramadol (n = 1), acetaminophen (n = 1), and milnacipran (n = 1). None of the patients were taking strong opioids 3 months postoperative. The temporal patterns and neuropathic components of the CPSP in the 2 groups are shown in Table 5.

Discussion

Although nefopam has been reported to have postoperative opioid-sparing and analgesic effects, its

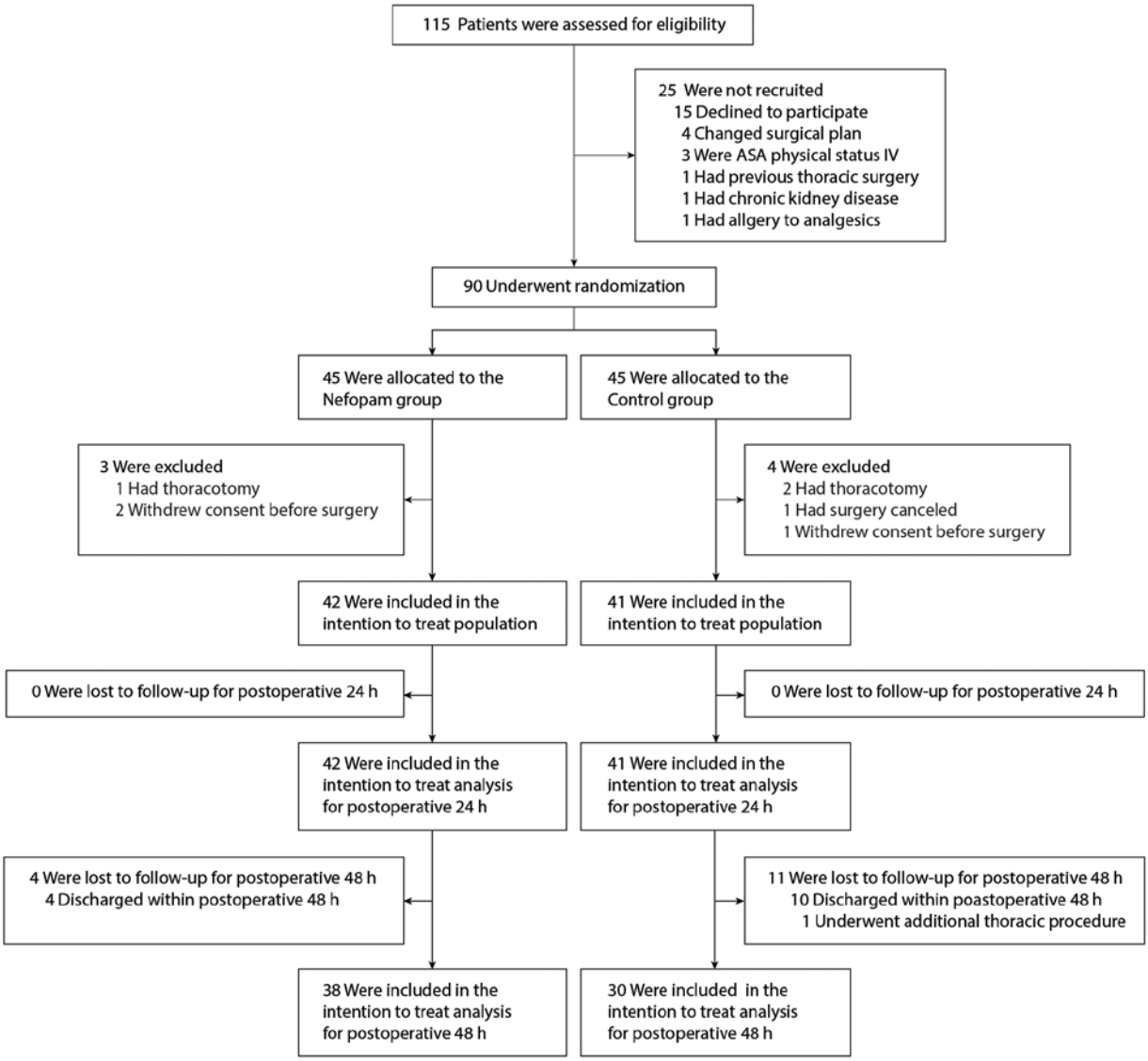

Fig. 1. *Consolidated Standards of Reporting Trials flow diagram for patient enrolment.*
ASA, American Society of Anesthesiologists.

effectiveness in patients who undergo VATS remains unclear. This study found a significant opioid-sparing effect of perioperative nefopam infusion using a dual-channel elastomeric infusion pump in patients undergoing VATS for lung cancer resection. Pain intensity during coughing at 48 hours postoperative was also significantly lower in the N group. However, perioperative nefopam infusion neither improved the postoperative quality of recovery nor reduced the occurrence of analgesic-related side effects, length of hospital stay, and occurrence of CPSP. In summary, the clinical effect of perioperative nefopam infusion beyond its opioid-sparing effect in these patients is debatable and further discussion of its clinical significance is required.

Our results are consistent with those of previous studies in which nefopam had an opioid-sparing effect in the postoperative period. One systematic review of 6 studies reported that nefopam significantly reduced cumulative morphine consumption by almost 30% during the first postoperative 24 hours (19). However, the small number of the clinical trials included in this review precluded a robust conclusion regarding the

Table 1. *Baseline patient characteristics.*

	Control group (n = 41)	Nefopam group (n = 42)	*P* value
Women	23 (56.1)	21 (50.0)	0.736
Age, year	62 (58-68)	67 (59–71)	0.189
Height, cm	160.1 ± 6.5	160.4 ± 8.6	0.847
Weight, kg	60.9 ± 9.7	63.9 ± 11.8	0.204
BMI, kg/m^2	23.5 (21.8–25.1)	24.6 (22.4–26.4)	0.215
ASA physical status, I/II	22 (53.7)/19 (46.3)	20 (47.6)/22 (52.4)	0.741
Preoperative QoR-15K (0-150)	145 (137–150)	143 (135–149)	0.365
Type of surgery			0.190
VATS wedge resection	5 (12.2)	1 (2.4)	
VATS segmentectomy	6 (14.6)	9 (21.4)	
VATS lobectomy	30 (73.2)	32 (76.2)	
Duration of surgery, min	105 (85–125)	115 (100–135)	0.020
Intraoperative remifentanil use, mcg/kg/hr	7.5 (3.9–12.4)	7.7 (3.3–13.1)	0.081

The values are presented as the mean ± standard deviation or median (interquartile range) or number (%). ASA, American Society of Anesthesiologists; BMI, body mass index; QoR-15K, Korean version of the Quality of Recover-15; VATS, video-assisted thoracic surgery

opioid-sparing effect of nefopam. A subsequent review that included more studies (10 randomized controlled trials of moderate or severe postoperative pain) similarly reported that nefopam showed a reproducible opioid-sparing effect, with 8/10 studies reporting such a finding (20).

However, no studies have investigated the opioid-sparing and analgesic effects of nefopam under multimodal analgesia. Both groups in the current study received preemptive intercostal nerve blockade and early routine administration of oral acetaminophen/tramadol combination tablets, as well as fentanyl-based IV-PCA. Even under this multimodal analgesia protocol, continuous infusion of nefopam up to 24 hours postoperative showed

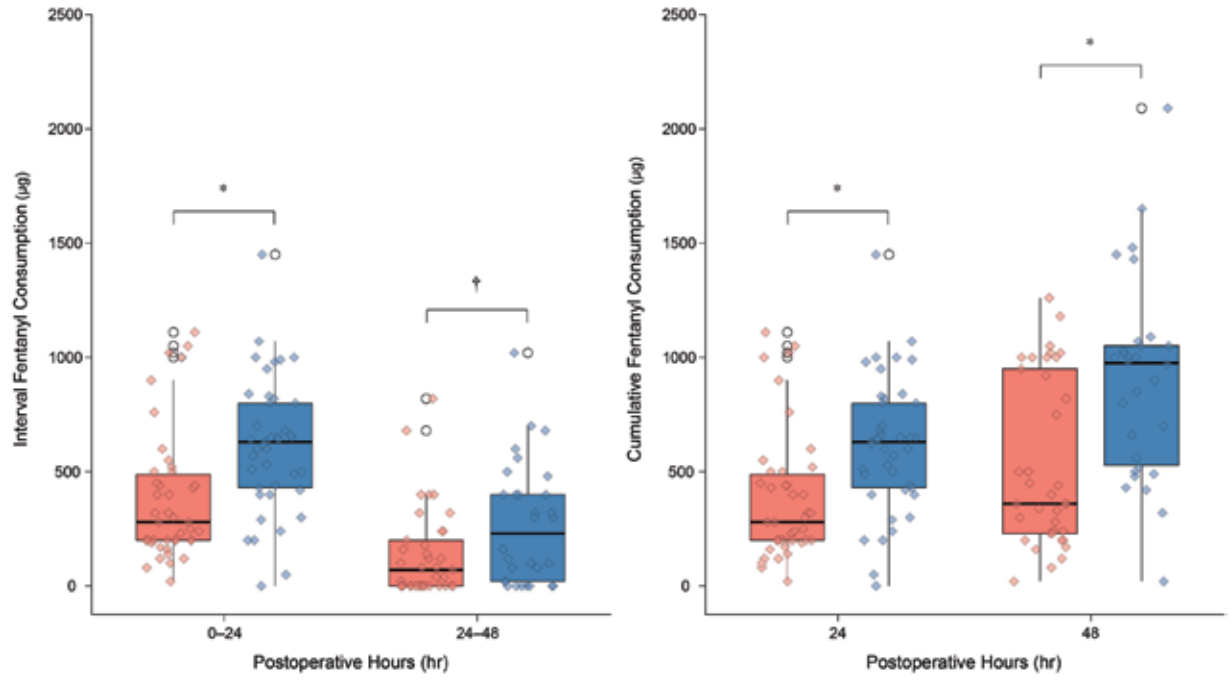

Fig. 2. *Between-group comparisons of the intravenous fentanyl consumption intervals. Box plot shows the median (interquartile range) fentanyl consumption in the 2 groups during the postoperative 48 hour period. Upper and lower whiskers are the maximum and minimum values, excluding outliers, respectively. Round symbols show the outliers. Scatter plot (diamond symbols) shows the individual data points. *P < 0.001, † P = 0.035 by Mann-Whitney U test.*

Table 2. *Between-group comparison of the Korean version of the Quality of Recovery-15 (QoR-15K) score, pain score at rest and during coughing, and rescue analgesic use.*

	Control group (n = 41)	Nefopam group (n = 42)	Median or % differencea (corrected 95% CI)[a]	Corrected *P* value [c]
Postoperative QoR-15K (0-150)				
24 h	111 (95–126)	117 (98–136)	5.5 (-12.5 to 25.5)	0.572
48 h [b]	119 (108–133)	122 (111–140)	3 (-9.5 to 17)	0.778
Pain score at rest, NRS-11 (0-10)				
24 h	4 (3–6)	3 (2–5)	-1 (-2 to 0)	0.146
48 h [b]	3 (2–5)	2 (0–3)	-1 (-2.5 to 1)	0.234
Pain score during coughing, NRS-11 (0-10)				
24 h	6 (5–8)	5 (4–6)	-1 (-2.5 to 0)	0.040
48 h [b]	5 (4–7)	5 (3–6)	-1 (-1.5 to 1)	0.842
Rescue analgesic use				
0–24 h	4 (9.8)	5 (11.9)	0.02 (-0.13 to 0.17)	> 0.999
24–48 h[b]	4 (13.3)	4 (10.8)	-0.03 (-0.21 to 0.15)	> 0.999

The values are presented as the median (interquartile range) or number (%). CI, confidence interval; NRS-11, numeric rating scale
[a] Median or % differences are expressed as the nefopam group versus the control group.
[b] This included 38 patients in the nefopam group and 30 patients in the control group.
[c] Bonferroni adjustments with corrections of the 95%CI were applied to multiple comparisons. A Bonferroni corrected $P < 0.05$ was considered statistically significant.

a significant opioid-sparing effect during the first postoperative 48 hours without increased analgesic-related adverse effects. Given that opioid use during hospitalization can be a significant predictor of persistent postoperative opioid use (21), the opioid-sparing effect of nefopam will be more meaningful in some Western countries with opioid crises (22).

However, despite its significant opioid-sparing effect, perioperative nefopam infusion did not significantly improve early postoperative outcomes other than pain intensity during coughing at postoperative 48 hours. The lack of additional significant benefits with respect to pain intensity could be because patients were allowed liberal IV-PCA use and that multimodal analgesia was performed in both groups. Additionally, because nefopam has also been reported to be emetogenic (23), its opioid-sparing effect could not lead to a significant difference in the occurrence of PONV in our modest sample size.

The aforementioned systematic review also reported that the use of nefopam was not significantly associated with the occurrence of opioid-related adverse effects such as PONV, sedation, and drowsiness; however, it was significantly associated with higher rates of hidrosis and tachycardia (19). Multimodal PONV prophylaxis consisting of the 5-HT3R antagonist, dexamethasone, and TIVA, which was given to our patients, may also have affected this insignificant difference in PONV occurrence. Furthermore, fentanyl, which we used in IV-PCA, is known to cause fewer opioid-related complications than morphine (24). As such, despite the significant opioid-sparing effect of perioperative nefopam infusion, it would have been difficult to achieve significant differences in opioid-related complications under our modest sample size. Therefore, under our current perioperative management, there would have been a small possibility of the opioid-sparing effect of perioperative nefopam improving the postoperative quality of recovery.

With respect to the effect of perioperative nefopam on CPSP, there was no significant difference in the occurrence of CPSP at postoperative 3 months between the N and C groups. We expected perioperative nefopam to reduce CPSP owing to its unique analgesic and antihyperalgesic effects compared with other nonopioid analgesics (10,25). Given that nefopam can reduce long-term potentiation in pain pathways mediated by the N-methyl-D-aspartate receptor (10,26), it could reduce central sensitization, which plays a pivotal role in the development of CPSP (27). Additionally, nefopam can prevent the development of CPSP by modulating descending pain pathways through alterations in neurotransmitters such as serotonin, norepinephrine, and dopamine (10,28).

However, previous clinical studies have shown conflicting results regarding the benefits of nefopam on

Table 3. *Between-group comparison of the rates of opioid or nefopam-related side effects, major postoperative complications, and the length of hospital stay.*

	Control group (n = 41)	Nefopam group (n = 42)	Median or % differencea (corrected 95% CI)[a]	Corrected *P* value
Nausea				
0–24 h	19 (46.3)	14 (33.3)	-0.13 (-0.37 to 0.11)	0.444 [d]
24–48 h [b]	8 (26.7)	6 (15.8)	-0.11 (-0.33 to 0.12)	0.554 [d]
Vomiting				
0–24 h	7 (17.1)	3 (7.1)	-0.10 (-0.26 to 0.06)	0.324 [d]
24–48 h [b]	2 (6.7)	1 (2.6)	0.02 (-0.09 to 0.13)	> 0.999 [d]
Rescue anti-emetic use				
0–24 h	8 (19.5)	6 (14.3)	-0.05 (-0.24 to 0.13)	> 0.999 [d]
24–48 h [b]	4 (13.3)	2 (5.3)	-0.08 (-0.24 to 0.08)	0.523 [d]
Hydrosis				
0–24 h	3 (7.3)	8 (19.0)	0.12 (-0.05 to 0.28)	0.216 [d]
24–48 h [b]	3 (10.0)	4 (10.5)	0.01 (-0.16 to 0.17)	> 0.999 [d]
Palpitation				
0–24 h	2 (4.9)	5 (11.9)	0.07 (-0.06 to 0.21)	> 0.999 [d]
24–48 h [b]	0 (0)	3 (7.9)	0.08 (-0.02 to 0.18)	0.654 [d]
Sedation				
0–24 h	2 (4.9)	7 (16.7)	0.12 (-0.03 to 0.27)	0.154 [d]
24–48 h [b]	2 (6.7)	8 (21.1)	0.14 (-0.04 to 0.32)	0.146 [d]
Major postoperative complications[c]	7[e] (17.1)	5[f] (14.3)	-0.05 (-0.20 to 0.10)	0.503
Length of hospital stay, days	3 (2–4)	4 (3–6)	1 (-0.5 to 2.7)	0.095

The values are presented as the median (interquartile range) or number (%). CI, confidence interval; NRS-11, numeric rating scale
[a] Median or % differences are expressed as the nefopam group versus the control group.
[b] This included 38 patients in the nefopam group and 30 patients in the control group.
[c] Major postoperative complications defined as the Clavien-Dindo classification grade III or higher within 7 days postoperatively.
[d] Bonferroni adjustments with corrections of the 95%CI were applied to multiple comparisons. A Bonferroni corrected $P < 0.05$ was considered statistically significant.
[e] This included postoperative pneumonia (n = 3), prolonged air leak (n = 2), chylothorax (n = 1), and supraventricular tachycardia requiring intensive care unit management (n = 1).
[f] This included postoperative pneumonia (n = 3), prolonged air leak (n = 1), and chylothorax (n = 1).

Table 4. *Between-group comparison of rates of adjuvant chemotherapy within 3 months postoperative and occurrence of overall chronic postsurgical pain (CPSP), CPSP with numeric rating scale score ≥ 3, and chronic use of analgesics.*

	Total (n = 82)	Control group (n = 41)	Nefopam group (n = 41)	% difference a (corrected 95% CI)[a]	Corrected *P* value
AC within 3 months postoperatively	14 (17.1)	5 (12.2)	9 (22.0)	-	-
Overall CPSP	36 (43.9)	18 (43.9)	18 (43.9)	0 (-0.26 to 0.26)	> 0.999 [b]
CPSP, NRS-11 ≥ 3	15 (18.3)	7 (17.1)	8 (19.5)	0.02 (-0.18 to 0.23)	> 0.999 [b]
Chronic use of analgesics	10 (12.2)	5 (12.2)	5 (12.2)	0 (-0.17 to 0.17)	> 0.999 [b]

The values are presented as the number (%). AC, adjuvant chemotherapy; CPSP, chronic postsurgical pain; NRS-11, numeric rating scale
[a] % differences are expressed as the nefopam group versus the control group.
[b] Bonferroni adjustments with corrections of the 95%CI were applied to multiple comparisons. A Bonferroni corrected $P < 0.05$ was considered statistically significant.

Table 5. *Between-group comparison of temporal pattern and neuropathic component of chronic postsurgical pain (CPSP).*

	Total	Nefopam group (n = 41)[a]	Control group (n = 41)
Temporal pattern			
Persistent pain with slight fluctuations	9 (10.8)	6 (14.3)	3 (7.3)
Persistent pain with pain attacks	7 (8.4)	3 (7.1)	4 (9.8)
Pain attacks without pain between them	19 (22.9)	8 (19.0)	11 (26.8)
Pain attacks with pain between them	1 (1.2)	1 (2.4)	0
Neuropathic component [b]	36 (43.4)	17 (40.5)	19 (46.3)

The values are presented as the number (%).
[a] One participant in the nefopam group died at postoperative day 28 due to acute respiratory distress syndrome.
[b] Neuropathic component included the following symptoms: burning or tingling sensation, sharp and shocking pain, hyperalgesia, allodynia, and numbness.

the occurrence of CPSP (29-31). One randomized controlled study that investigated the effect of perioperative nefopam on postoperative hyperalgesia reported that nefopam administration reduced hyperalgesia in the early postoperative period. However, that effect was not maintained after the end of its administration (31). The authors assumed that the effect of nefopam on pain sensitization might have been inadequate to decrease the occurrence of CPSP. Our results also support this assumption.

This study had some limitations that need to be considered in the interpretation of the results. First, the findings have limited generalizability as they were obtained from a single institution. Second, we did not consider the type of surgery at randomization; thus, there was bias toward a higher rate of wedge resections in group C. This might have resulted in a significant difference in the duration of surgery between the 2 groups and could have affected the length of hospital stay and the proportion of adjuvant chemotherapy within the postoperative 3 month period. Third, the institutional protocol for discharge eligibility in patients who have undergone VATS is mainly based on chest tube removal. Therefore, the analgesic and opioid-sparing effect of perioperative nefopam infusion would have been unlikely to affect the length of hospital stay. Fourth, our multimodal analgesia protocol had room for improvement, such as intravenous acetaminophen administration during the perioperative period, which might have affected the results of our study. Last, despite our routinely administering serotonergic drugs such as fentanyl, 5-HT3 antagonists, and tramadol in our patients, we did not investigate serotonin syndrome-related symptoms, which can be caused by the co-administration of nefopam and these drugs (32). Physicians must be careful about the potential risk of serotonin syndrome when co-administering these drugs. Despite these limitations, to the best of our knowledge, this study is the first to evaluate the opioid-sparing effect of perioperative nefopam under multimodal analgesia in patients undergoing VATS.

Conclusion

In conclusion, perioperative nefopam infusion using a dual-channel elastomeric infusion pump provides a significant opioid-sparing effect under multimodal analgesia in patients with lung cancer undergoing VATS. Therefore, it is a feasible option for multimodal analgesia in patients undergoing thoracic surgery. However, this benefit did not lead to significant improvements in other postoperative outcomes under multimodal analgesia.

Author's contribution

Susie Yoon: This author contributed to study design/planning, data collection, data analysis, and drafting the manuscript.

Hyo Bin Lee: This author contributed to data collection and data analysis.

Kwon Joong Na: This author contributed to data collection and revising the manuscript.

Samina Park: This author contributed to data collection and revising the manuscript.

Jaehyon Bahk: This author contributed to data analysis and revising the manuscript.

Ho-Jin Lee: This author contributed to study design/planning, data collection, data analysis, and revising the manuscript.

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