Original Article

Nefopam as a multimodal analgesia in thoracoscopic surgery: a randomized controlled trial

Hyun-Seo Ki[1#], Jae-Geum Shim[1], Hyung-Kyeong Choi[1], Kyoung-Ho Ryu[1#], Du-Young Kang[2], Jiyeon Park[1], Jin Hee Ahn[1], Sung Hyun Lee[1], Eun-Ah Cho[1]^

[1]Department of Anesthesiology and Pain Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Thoracic and Cardiovascular Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Contributions: (I) Conception and design: EA Cho, KH Ryu; (II) Administrative support: HK Choi, JG Shim, SH Lee; (III) Provision of study materials or patients: DY Kang; (IV) Collection and assembly of data: DY Kang, HS Ki, J Park; (V) Data analysis and interpretation: EA Cho, HS Ki, JH Ahn; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Eun-Ah Cho, PhD. Department of Anesthesiology and Pain Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Republic of Korea. Email: chaosea@skku.edu.

Background: Video-assisted thoracoscopic surgery (VATS) is a minimally invasive procedure. However, some patients still experience severe pain after VATS. Pain after VATS can disturb deep breathing and coughing, and can increase postoperative pulmonary complications. Therefore, multidisciplinary pain management is emphasized for enhanced recovery after VATS. Nefopam is a centrally-acting, non-opioid, non-steroidal analgesic drug, and its pain reduction effect in many surgeries has been reported. We sought to determine whether administration of nefopam is effective as multimodal analgesia in VATS.

Methods: This study enrolled patients aged 19 years or older, and scheduled for elective VATS lobectomy with American Society of Anesthesiologists (ASA) physical class I–III. Forty-six participants were randomly divided into a group receiving nefopam (group N), and a control group (group O) in a 1:1 ratio. The study participants, and the researcher collecting the data were blinded to the group allocation. For the group N, nefopam 20 mg was administered before surgical incision and also at the end of surgery while chest tube was inserted. For the group O, normal saline 100 mL was administered. The primary outcome of this study was the pain score, by verbal numerical rating scale, at rest and upon coughing.

Results: Forty-five participants (group N =22, group O =23) were involved in the statistical analysis. Nefopam reduced pain at rest at 0 h [8 (IQR, 5–10) *vs.* 4 (IQR, 2–7), P=0.01], and at 0–1 h [5 (IQR, 5–8) *vs.* 3 (IQR, 2–5), P=0.001]. Pain upon coughing decreased with nefopam at 0 h [9 (IQR, 6–10) *vs.* 6 (IQR, 2–8), P=0.009], 0–1 h [6 (IQR, 5–8) *vs.* 5 (IQR, 2–6), P=0.001], and at 12–24 h [4 (IQR, 3–7) *vs.* 3 (IQR, 1–4), P=0.03]. Injection of 20 mg of nefopam before incision and at the end of surgery relieved postoperative pain at 0 h, 1 h at rest and at 0 h, 1 h, 12–24 h with coughing after VATS.

Conclusions: Therefore, nefopam can serve as a useful component of multimodal analgesia for pain management after VATS.

Trial Registration: ClinicalTrials.gov (NCT05173337).

Keywords: Nefopam; multimodal analgesia; thoracoscopic surgery; pain; analgesia

Submitted Jan 15, 2024. Accepted for publication Apr 26, 2024. Published online Jun 12, 2024.
doi: 10.21037/jtd-24-30
View this article at: https://dx.doi.org/10.21037/jtd-24-30

^ ORCID: 0000-0002-3445-1905.

Introduction

Video-assisted thoracoscopic surgery (VATS) is a minimally invasive thoracic surgical procedure (1). It provides better postoperative outcomes including less postoperative pain, shorter hospital stay, and less pulmonary function impairment compared to the open thoracotomy (2). However, patients still experience severe pain after VATS lobectomy, although less than open thoracotomy (3,4). Pain after lung surgery can interfere deep breathing and lung toileting, and can increase postoperative pulmonary complications. Moreover, uncontrolled pain might generate post-thoracotomy pain syndrome (5,6). Therefore, multidisciplinary pain management is emphasized for enhanced recovery after lung surgery (6).

Enhanced recovery after surgery (ERAS) protocol implements multimodal analgesia, which blocks diverse pain pathways, minimizing the side effects of each analgesic agents. In general, opioids are used in combination with other drugs such as nonsteroid anti-inflammatory drugs (NSAIDs), steroids, paracetamol, and gabapentinoids for postoperative pain control (1). However, it has not yet been established how to combine these drugs to ensure the best analgesic effect for VATS lobectomy.

Nefopam is a non-opioid, non-steroidal analgesic drug that acts at an N-methyl-D-aspartate (NMDA) receptor, and inhibits monoamine reuptake. It has antinociceptive and anti-hyperalgesic effects (7). Nefopam reduced exertional pain after intestinal surgery (8), reduced opioid consumption after hysterectomy (9), and postoperative pain after gastrectomy (10). However, its efficacy as a multimodal analgesic for VATS lobectomy is not well elucidated (11).

Highlight box

Key findings

- Nefopam, when used as a multimodal analgesia, reduced pain during the immediate period after surgery both at rest and during coughing.

What is known and what is new?

- There are several studies for evaluating efficacy of nefopam as a multimodal analgesic agent.
- This study demonstrated nefopam can serve as a useful component of multimodal analgesia for pain management after video-assisted thoracoscopic surgery (VATS).

What is the implication, and what should change now?

- Nefopam can serve as a useful component of multimodal analgesia for pain management after VATS.

In our study, we hypothesized that nefopam would be helpful in relieving postoperative pain after VATS lobectomy. Therefore, we aimed to investigate the efficacy of nefopam as a multimodal analgesia for pain reduction after VATS lobectomy. We present this article in accordance with the CONSORT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/rc).

Methods

Study participants

This randomized controlled study was conducted prospectively. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC IRB No. 2021-08-068), and registered at ClinicalTrials.gov (NCT05173337) prior to the study participant enrollment. Written informed consent was achieved from all study participants before their study participation. This study was conducted at the single tertiary hospital (Kangbuk Samsung Hospital, Seoul, Korea). This study enrolled patients aged nineteen years or older, and scheduled for elective VATS lobectomy with American Society of Anesthesiologists (ASA) physical class I–III. The patient with the one of the followings were excluded from the study: history of allergy to nefopam or NSAIDs, kidney dysfunction, liver dysfunction, myocardial infarction, closed angle glaucoma, pregnancy, woman on lactation, or disagreement to use intravenous-patient controlled analgesia (IV-PCA).

Randomization and blinding

The study participants were randomly divided into a group receiving nefopam (group N), and a group not receiving nefopam (group O) in a 1:1 ratio. The list produced by the randomization table which had been generated using a computer-generated randomization algorithm (http://www.randomization.com), and was kept in a sealed envelope in order. The patient was allocated to each group in order, on the day before surgery. The physician anesthetizing the study participants was aware of the study group, and administered nefopam according to the allocated group. The study participants, and the researcher collecting the data were blinded to the group allocation, throughout the whole study period.

Anesthetic procedure

No premedication was administered in all participants. The participants were kept fasted for more than 8 hours. Once they entered the operating room, standard anesthetic monitoring including noninvasive blood pressure measurement, electrocardiography, pulse oximeter, and electroencephalographic anesthetic depth monitoring (SedLine®, Masimo Corp., Irvine, CA, USA) were applied. After denitrogenating the participants with 100% oxygen for 3 min, the participants were anesthetized with propofol 1.5–2 mg/kg intravenous (IV), and remifentanil 1 mcg/kg IV. Endotracheal intubation was performed 2 min after the administration of rocuronium 1 mg/kg IV. The radial artery was catheterized with 20 G angiocath, and intravenous line was placed at the forearm with 18 G angiocath. Anesthesia was maintained with sevoflurane 1.5–2.5 vol%, targeting the patient state index 25–50. The participants were ventilated with 100% of oxygen before and 20 min after the start of one lung ventilation. Arterial blood gas analysis was conducted at 20 min after one lung ventilation. Fraction of inspired oxygen was lowered to 50% for those with pressure of arterial oxygen above 150 mmHg, while it was maintained 100% for those with pressure of arterial oxygen less than 150 mmHg. At the end of the surgery, ketorolac 30 mg IV, and pethidine 0.5 mg/kg IV were given to all study participants. After giving sugammadex 200 mg IV, the participants were extubated, and sent to the post-anesthesia care unit (PACU).

IV-PCA was used for all participants. The IV-PCA contained 1,200 mcg of fentanyl (mixed with normal saline, 120 mL in total). The background infusion was delivered at a rate of 1 mL/h, and 1 mL of bolus was permitted with 10 min of lock out time. The IV-PCA was connected to the patient's IV, and was started at the end of surgery. The IV-PCA was disconnected when the patient complained severe nausea or vomiting, or when the patient requested to discontinue.

Study protocol

For the group N, nefopam 20 mg mixed with normal saline 100 mL was administered before surgical incision, and at the end of surgery while chest tube was inserted. For the group O, normal saline 100 mL was administered before surgical incision, and at the end of surgery.

Outcome measures

The intensity of postoperative pain was assessed with verbal numerical rating scale (VNRS) graded from 0 (no pain) to 10 (the worst pain ever). The postoperative pain was measured in the resting state and after coughing. Pain assessment was performed after assessment of sedation level by 6-point Ramsay Sedation Score (RSS): 1, anxious and agitated or restless or both; 1, cooperative, oriented and tranquil; 3, responding to command only; 4, brisk response to light glabellar tap or loud auditory stimulus; 5, sluggish response to glabellar tap or loud auditory stimulus; and 6, no response to stimulus (12). The initial postoperative pain was evaluated within 5 min of arrival at PACU (0 h) after confirming the RSS 2. The postoperative pain was further evaluated during PACU stay (0–1 h), 1–6 h, 6–12 h, and 12–24 h. Participants were asked to recall the worst pain experienced during each period.

Participants with pain >4 on VNRS were treated with ketorolac 30 mg IV and those with pain >6 on VNRS were treated with tramadol 50 mg IV as rescue analgesics. The number of participants who received rescue analgesics was collected.

Cumulative amount of IV-PCA delivered to the participants over 1, 6, 12, and 24 h was collected. The duration of IV-PCA referred to the time intervals between its start and removal. The incidence of dizziness, and postoperative nausea and vomiting (PONV) was recorded. The incidence of tachycardia, defined by heartrate over 100 bpm, was also recorded.

For assessment of quality of recovery (QoR), QoR-15 score was used. QoR-15 consists of 15 questionnaires, each of which scores from 0 to 10 (150 in total). The higher the score, the higher the QoR. The QoR-15 is divided into 5 dimensions including, physical comfort, emotional state, psychological support, physical independence, and pain (13). QoR-15 was assessed at postoperative day 1.

Statistical analysis

Sample size was calculated based on our preliminary data (unpublished data). Resting VNRS after VATS lobectomy in group O and group N was 8.0±1.7, and 4.8±4.4, respectively. In a pilot study conducted by researchers, the pain scores after VATS in the control group (nefopam non-administration group) and the nefopam administration

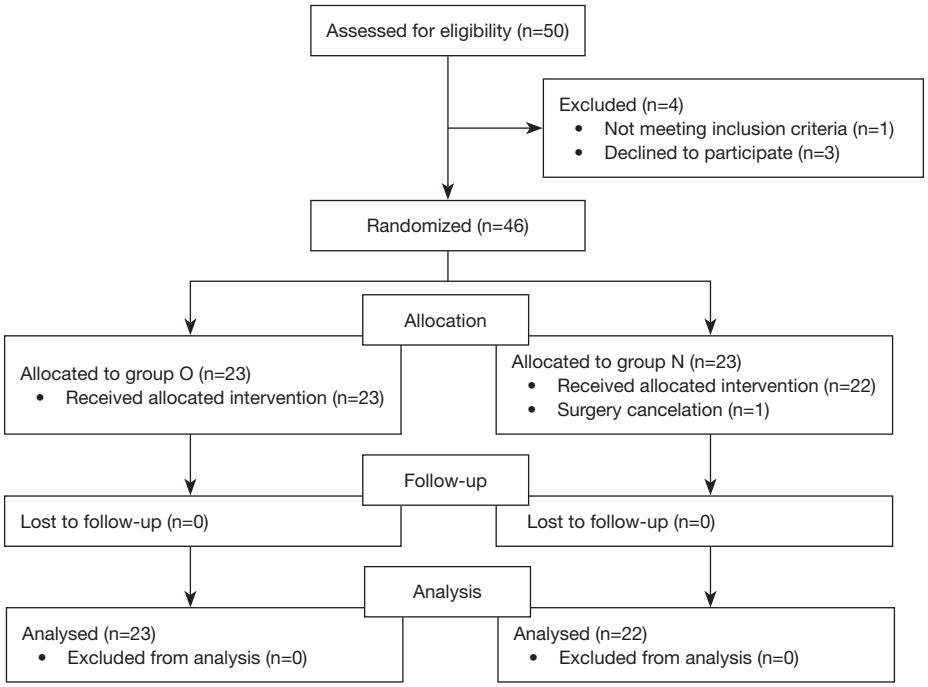

Figure 1 CONSORT flowgram of the study.

group were 8.0±1.7 and 4.8±4.4, respectively. With α value set at 0.05 and a power (1–β) of 0.8, the calculated minimum sample size for each group was 19, totaling 38 participants. Assuming a 20% dropout rate, the study was designed to have 46 patients, with 23 in each group.

Data are described as mean ± standard deviation (SD), median [interquartile range (IQR)], and number (%) as appropriate. Variables were compared between the two groups (group N *vs.* Group O). Continuous variables were compared using the t-test for normally distributed data, and the Mann-Whitney *U*-test for non-normally distributed data. Categorial data were compared using the Chi square test or Fishers exact test, as appropriate. The differences in means, medians, and proportions between the two groups, and their respective 95% confidence intervals (CIs) were reported. P<0.05 was determined to be statistically significant. Statistical analysis was performed using R version 4.2.2 (R Project for Statistical Computing; R Foundation for Statistical Computing, Vienna, Austria) and MedCalc® Version 20.211 (MedCalc Software Ltd. Ostend, Belgium).

Results

From December 2021 to September 2022, 50 patients were assessed for eligibility for the study participation. Among these, 1 patient who did not meet inclusion criteria, and three patients who declined to participate were excluded. Therefore, 46 patients were randomly allocated to the group N (n=22), and group O (n=23). One patient in the group N was dropped out of the study due to cancelation of the surgery related because of fever. Therefore, total 45 patients were included in the final analysis (*Figure 1*).

The baseline characteristics of the patients were not different between the two groups (*Table 1*). Postoperative pain, use of rescue analgesics, and IV-PCA data are described in the *Table 2*. Pain at rest was lower in the group N than group O at 0 h [4 (IQR, 2–7) *vs.* 8 (IQR, 5–10), median difference: −3 (95% CI: −5 to −1), P=0.01] and at 0–1 h [3 (IQR, 2–5) *vs.* 5 (IQR, 5–8), median difference: −3 (95% CI: −4 to −1), P=0.001]. Pain at rest at 1–6 h (P=0.61), 6–12 h (P=0.55), and 12–24 h (P=0.06) were not different between groups. Pain with coughing was lower in the group N compared to the group O at 0 h [6 (IQR, 2–8) *vs.* 9 (IQR, 6–10), median difference: −3 (95% CI: −5 to 0), P=0.009], 0–1 h [5 (IQR, 2–6) *vs.* 6 (IQR, 5–8), median difference: −3 (95% CI: −4 to −1), P=0.001], and at 12–24 h [3 (IQR, 1–4) *vs.* 4 (IQR, 3–7), median difference: −2 (95% CI: −3 to 0), P=0.03]. Pain with coughing was not different at 1–6 h (P=0.60), and 6–12 h (P=0.12). The use of rescue analgesics,

Table 1 Baseline demographic data of the study participants

Variables	Nefopam		P value
	No (n=23)	Yes (n=22)	
Age, years	60±9	64±12	0.32
Sex, male/female			0.63
Male	11 (47.8)	8 (36.4)	
Female	12 (52.2)	14 (63.6)	
Body mass index, kg/m^2	24.5±3.4	24.8±3.1	0.79
ASA PS			0.49
I	4 (17.4)	3 (13.6)	
II	13 (56.5)	16 (72.7)	
III	6 (26.1)	3 (13.6)	
Diabetes mellitus	4 (17.4)	4 (18.2)	>0.99
Hypertension	7 (30.4)	8 (36.4)	0.92
Smoking			0.07
Ex-smoker	7 (30.4)	1 (4.5)	
Smoker	2 (8.7)	2 (9.1)	
Non-smoker	14 (60.9)	19 (86.4)	
Intraoperative data			0.67
Left	7 (30.4)	9 (40.9)	
Right	16 (69.6)	13 (59.1)	
Converted to open procedure	5 (21.7)	5 (22.7)	>0.99
Estimated blood loss, mL	70 [50–100]	80 [60–130]	0.24
Fluid, mL	1,000 [900–1,375]	1,400 [1,100–1,550]	0.052
Urine output, mL	270 [103–450]	300 [180–460]	0.38
Remifentanil, mcg	480 [320–700]	480 [360–790]	0.63
Duration of surgery, min	126±46	140±44	0.32
Duration of anesthesia, min	184±55	201±48	0.29
Duration of one lung ventilation, min	114±42	129±46	0.26

Data are presented as mean ± standard deviation, median [interquartile range], or numbers (%). ASA PS, American Society of Anesthesiologists physical status.

cumulative IV-PCA use, IV-PCA duration, and the number of patients with discontinuation of IV-PCA due to side effect were not different between the two groups. In a subgroup analysis including VATS only patient, pain scores in group N was lower than group O at postoperative 0 h, 0–1 h, and 12–24 h, both at rest (P=0.009, <0.001, and 0.01, respectively) and during coughing (P=0.01, <0.001, and 0.04, respectively; Table S1).

Postoperative QoR-15 are shown in the *Table 3*. Among each item, group N [8 (IQR, 8–10)] scored higher for the item number 1 (able to breath easily) compared to the group O [8 (IQR, 6–8), median difference: 1 (95% CI: 0–2), P=0.04]. QoR-15 by 5 dimensions and global QoR-15 were not different between two groups. In a subgroup analysis

Table 2 The worst pain (VNRS) at rest, and with coughing, use of rescue analgesics, cumulative IV-PCA use within 24 h after surgery

Outcomes	Nefopam		Difference (95% CI)	P value
	No (n=23)	Yes (n=22)		
Pain at rest, VNRS				
0 h	8 [5–10]	4 [2–7]	–3 (–5 to –1)	0.01*
0–1 h	5 [5–8]	3 [2–5]	–3 (–4 to –1)	0.001*
1–6 h	2 [2–4]	3 [2–4]	0 (–1 to 1)	0.61
6–12 h	2 [1–4]	2 [1–3]	0 (–1 to 1)	0.55
12–24 h	2 [1–4]	1 [1–2]	–1 (–2 to 0)	0.06
Pain with coughing				
0 h	9 [6–10]	6 [2–8]	–3 (–5 to 0)	0.009*
0–1 h	6 [5–8]	5 [2–6]	–3 (–4 to –1)	0.001*
1–6 h	5 [4–8]	5 [4–6]	0 (–2 to 1)	0.60
6–12 h	5 [4–7]	4 [3–6]	–1 (–2 to 0)	0.12
12–24 h	4 [3–7]	3 [1–4]	–2 (–3 to 0)	0.03*
Rescue analgesics				
0–1 h	5 [21.7]	3 [13.6]	8.1 (–15.0 to 30.1)	0.70
1–6 h	4 [17.4]	6 [27.3]	9.9 (–14.4 to 33.2)	0.49
6–12 h	8 [34.8]	9 [40.9]	6.1 (–20.8 to 32.0)	0.67
12–24 h	13 [56.5]	12 [54.5]	2.0 (–25.1 to 28.7)	>0.99
Cumulative IV-PCA, mL				
~1 h	0	0 [0–5]	0 (0 to 2)	0.20
~6 h	10 [5–15]	15 [5–16]	0 (–5 to 5)	0.80
~12 h	22 [16–30]	20 [12–30]	–2 (–10 to 5)	0.44
~24 h	39 [25–45]	35 [20–50]	–5 (–15 to 10)	0.60
IV-PCA duration, min	828±372	976±415	–148 (–415 to 119)	0.27
Discontinuation of IV-PCA due to side effect	7 (30.4)	5 (22.7)	7.7 (–11 to 33.3)	0.81

Data are presented as mean ± standard deviation, median (interquartile range), or numbers (%). *, P<0.05. VNRS, verbal numerical rating scale; IV-PCA, intravenous-patient controlled analgesia; CI, confident interval.

including VATS only item number 1 was better in group N than group O (P=0.01, Table S2). Postoperative dizziness and PONV showed no statistically significant difference (*Table 4*).

Discussion

In this study we sought to determine whether adding nefopam to a combination of opioid and ketorolac is effective as multimodal analgesia in VATS. Nefopam, when used as a multimodal analgesia, reduced pain at rest at 0 h [8 (IQR, 5–10) *vs.* 4 (IQR, 2–7), P=0.01], and at 0–1 h [5 (IQR, 5–8) *vs.* 3 (IQR, 2–5), P = 0.001]. Pain upon coughing decreased with nefopam at 0 h [9 (IQR, 6–10) *vs.* 6 (IQR, 2–8), P=0.009], 0–1 h [6 (IQR, 5–8) *vs.* 5 (IQR, 2–6), P=0.001], and at 12–24 h [4 (IQR, 3–7) *vs.* 3 (IQR, 1–4), P=0.03]. Among 15 items of QoR-15, it was reported that group N was more able to breathe easily compared to group O (P=0.04).

Although VATS is a minimally invasive procedure, it can still cause moderate to severe pain (4). Severe pain

Table 3 Postoperative QoR-15 score

Variables	Nefopam		Median difference (95% CI)	P value
	No (n=23)	Yes (n=22)		
QoR-15 by each item				
1. Able to breath easily	8 [6–8]	8 [8–10]	1 (0 to 2)	0.04*
2. Been able to enjoy food	8 [5–10]	9 [7–10]	0 (0 to 2)	0.30
3. Feeling rested	8 [6–10]	9 [7–10]	0 (–1 to 2)	0.55
4. Have had a good sleep	7 [3–9]	8 [6–9]	1 (–1 to 3)	0.26
5. Able to look after personal toilet and hygiene unaided	8 [7–10]	8 [6–10]	0 (–2 to 1)	0.75
6. Able to communicate with family or friends	10 [9–10]	10 [9–10]	0 (0 to 0)	0.38
7. Getting support from hospital doctors and nurses	10 [10–10]	10 [9–10]	0 (–1 to 0)	0.12
8. Able to return to work or usual home activities	5 [3–8]	6 [4–8]	1 (–1 to 3)	0.37
9. Feeling comfortable and in control	9 [7–10]	8 [8–10]	0 (–2 to 1)	0.70
10. Having a feeling of general well-being	7 [5–8]	8 [6–10]	1 (0 to 3)	0.11
11. Moderate pain	5 [3–9]	6.5 [4–7]	0 (–2 to 2)	0.65
12. Severe pain	8 [7–10]	8 [4–10]	0 (–2 to 1)	0.37
13. Nausea or vomiting	9 [4–10]	10 [9–10]	0 (0 to 2)	0.17
14. Feeling worried or anxious	8 [4–10]	9 [6–10]	0 (–1 to 2)	0.50
15. Feeling sad or depressed	9 [7–10]	10 [6–10]	0 (–1 to 1)	0.92
QoR-15 by dimensions				
Emotional state	30 [23–37]	30 [26–38]	1 (–4 to 6)	0.75
Psychological support	20 [18–20]	20 [18–20]	0 (–1 to 0)	0.24
Physical independence	13 [10–15]	14 [10–18]	0 (–3 to 4)	0.75
Physical comfort	37 [29–44]	43 [37–45]	4 (0 to 10)	0.07
Pain	14 [11–18]	13 [8–16]	–1 (–4 to 2)	0.45
Global QoR-15	109 [99–122]	118 [103–129]	7 (–6 to 17)	0.28

Data are presented as median [interquartile range]. *, P<0.05. QoR, quality of recovery; CI, confident interval.

immediately after VATS can delay postoperative recovery by disrupting effective deep breathing and coughing (11). Furthermore, intense pain in acute postoperative period is strongly associated with chronic post thoracotomy pain syndrome, which impairs the quality of life (14). Therefore, various multimodal approaches have been introduced to reduce pain after VATS. While regional analgesia, such as thoracic epidural analgesia, or paravertebral block, is reported to be effective in controlling the pain, it comes with risks of pneumothorax, bleeding, local anesthetic toxicity, and hypotension (4,15,16). Although, studies on multimodal analgesia involving variety of medications have been consistently conducted, a gold standard method for pain control in VATS has not yet been established (4).

Nefopam is an analgesic for neuropathic pain that acts centrally by inhibiting reuptake of serotonin, norepinephrine, and dopamine (17). It also prevents neuropathic pain by blocking neural sensitization by downregulating the phosphor-c-Jun N-terminal kinase and autophagy, and by modulation of immune response (18). These mechanisms allow nefopam to serve as a pre-emptive analgesia for alleviating postoperative pain, and it may offer long-term assistance in preventing chronic pain (19). There are several studies for evaluating efficacy of nefopam as a multimodal analgesic agent in different types of surgery (10,20,21). In laparoscopic gastrectomy, 20 mg of nefopam administered

Table 4 Postoperative recovery profiles and complications including dizziness, and postoperative nausea and vomiting, tachycardia, and pneumonia

Outcomes	Nefopam		Difference (95% CI)	P value
	No (n=23)	Yes (n=22)		
Length of hospital stay, days	8 [6–11]	9 [6–9]	–1 (–8.4 to 5.4)	0.79
Pneumonia	1 (4.3)	1 (4.5)	–0.2 (–8.5 to 11.8)	>0.99
Dizziness				
0 h	2 (8.7)	1 (4.5)	4.2 (–7.3 to 18.6)	>0.99
1 h	3 (13.0)	0	13.0 (7 to 26.7)	0.23
6 h	7 (30.4)	6 (27.3)	3.1 (15.7 to 29.6)	0.82
12 h	5 (21.7)	6 (27.3)	–5.6 (22.4 to 19.5)	0.67
24 h	9 (39.1)	6 (27.3)	11.8 (8.1 to 39.1)	0.40
PONV				
0 h	1 (4.3)	1 (4.5)	–0.2 (–8.5 to 11.8)	>0.99
1 h	0	1 (4.5)	–4.5 (–4.5 to 4.2)	0.49
6 h	7 (30.4)	2 (9.1)	21.3 (2.5 to 43.6)	0.14
12 h	4 (17.4)	1 (4.5)	12.9 (–2.6 to 30.7)	0.35
24 h	6 (26.1)	3 (13.6)	12.5 (–5.4 to 35.5)	0.46
Tachycardia*				
0 h	0	0	0 (0 to 0)	N/A
1 h	0	0	0 (0 to 0)	N/A
6 h	0	0	0 (0 to 0)	N/A
12 h	0	0	0 (0 to 0)	N/A
24 h	0	2 (9.1)	–0.091 (–0.091 to 0.029)	0.78

Data are presented as median [interquartile range] or numbers (%). *, tachycardia is defined by heartrate over 100 bpm. N/A, not applicable; CI, confident interval; PONV, postoperative nausea and vomiting.

after anesthesia induction and at the end of surgery reduced intraoperative remifentanil use, pain score in the PACU, and postoperative IV-PCA use during the first 6 h after surgery (10). Likewise, intravenous nefopam resulted in significant reduction in postoperative pain scores and opioid requirements while decreasing opioid-related adverse effects in laparoscopic cholecystectomy (21). When nefopam 240 mg was combined with fentanyl 600 mcg in the IV-PCA, there was no significant difference in postoperative pain scores observed in laparoscopic cholecystectomy compared to using fentanyl 1,200 mcg alone in IV-PCA (20). In arthroscopic shoulder surgery, nefopam 120 mg provided similar analgesic effect to those provided by ketorolac 2 mg/kg when mixed in IV-PCA (22).

Whilst some previous studies suggest nefopam as part of multimodal analgesia for postoperative pain control, the efficacy of nefopam in VATS surgery is not fully elucidated (11,17). Yeo *et al.* demonstrated that administering 20 mg of nefopam before incision and 15 min before the end of surgery did not reduce cumulative opioid consumption during the 6 hours following VATS, when co-administered with 0.01 mg/kg of hydromorphone and 1 g of acetaminophen (11). On the other hand, Yoon *et al.* reported that a continuous infusion of 60 mg of nefopam for 48 hours postoperatively, followed by 20 mg of nefopam after anesthesia induction, resulted in reduced fentanyl consumption in the first 24 h after VATS (17).

Nefopam, when administered in conjunction with non-steroidal anti-inflammatory drugs or opioids, exhibits a synergistic interaction that enhances the analgesic effects

of each medication (23). Hence, we administered 20 mg of nefopam before incision, and at the end of surgery in conjunction with ketorolac 30 mg and pethidine 0.5 mg/kg. However, in our study, there was no opioid-sparing effect, reduction in IV-PCA usage, or pain relief in the nefopam group at 6, 12, or 24 h postoperatively. This corresponds with the previous study that showed no opioid-sparing effect with double bolus administration of nefopam during the 6 h following VATS (11). Considering the opioid-sparing effect observed with continuous infusion in study by Yoon *et al.*, it can be inferred that double bolus administration of nefopam may be insufficient in providing adequate postoperative analgesia after VATS compared to continuous infusion (17). Furthermore, Yoon *et al.* administered a total of 80 mg of nefopam over 48 hours, whereas in our study, 40 mg of nefopam was used only during surgery (17). Therefore, both the duration of administration and the total dosage of nefopam may have had an impact on its postoperative analgesic effect in our study. However, further research addressing suitable dosing regimens and administration methods is imperative to support this.

In our study, the analgesic effect in the nefopam group was short-lived, lasting only up to 1 h after surgery. Although a difference was observed at 12–24 h post-surgery, it does not seem clinically significant demonstrating a score of 2 in group O and 1 in group N. We hypothesized the following reasons for this outcome: first, the half-life of nefopam is 5.1±0.6 h after intravenous administration (24). Therefore, its analgesic efficacy maybe decreased at 5–6 h after surgery. The expectation for administration of nefopam is for its anti-hyperalgesic effect. In other words, nefopam blocks voltage-sensitive calcium and sodium channels, which modulates glutamatergic transmission at the central level (25). The anti-hyperalgesic effect of nefopam is controversial depending on the type of surgery it was used for and its regimen (10,20-22). Therefore, we believe that giving 20 mg of nefopam twice, before incision and at the end of surgery, was not be enough to show its anti-hyperalgesic effect on VATS. Second, the pain score in the control group was too low to make difference with nefopam group. This may because the surgery itself was minimally invasive. Furthermore, patients began receiving analgesics starting from 6 hours post-surgery (up to 56.6%). Therefore, these factors might have caused less difference between the two groups.

Our study demonstrated a decrease in postoperative pain during the immediate period after surgery both at rest and during coughing. The severe postoperative pain experienced immediately in the PACU, combined with incomplete arousal from anesthesia, can lead to agitation and worsen postoperative recovery (26). Furthermore, the intensity of pain immediately after surgery in the PACU is correlated with the development of chronic pain (14,27). Therefore, even though there was no significant difference in pain up to 24 h after surgery between the two groups, we believe that reduction in immediate pain in the group N is noteworthy. However, considering its short-lived effect, exploring continuous administration of nefopam in future studies is needed to determine if it could potentially enhance its efficacy in postoperative pain management. Furthermore, since we did not investigate the occurrence of chronic pain in our study, we cannot assure whether double bolus of nefopam will helpful in preventing chronic post thoracotomy pain syndrome.

In our study, we assessed QoR-15 to evaluate the effect of nefopam on the subjective satisfaction of the patients. The patients in the group N had higher scores in the item assessing whether breathing was easy after surgery. However, there was no difference between the two groups in terms of global QoR-15 scores or QoR-15 by dimension. Given that deep breathing plays a pivotal role in the recovery process following lung resection surgery, the improvement in respiratory comfort observed in group N holds significant relevance. However, as previously mentioned, the effectiveness of nefopam appeared to be limited to immediate postoperative pain, which may explain the absence of favorable outcomes in other items of QoR-15 questionnaire.

There were a few limitations in this study. First, our study included cases where VATS had to be converted to open thoracotomy. Open thoracotomy typically results in significantly more intense postoperative pain compared to VATS. Therefore, the general pain scores in our study may be higher compared to when only VATS patients were included. However, since our study did not show a significant difference in the conversion rate to open thoracotomy between the two groups, it may have had little effect on the results. Additionally, as open thoracotomy patients constitute approximately 20% of our study population, caution is needed when extrapolating our pain scores to patients who underwent VATS only. Second, because our study examined data only up to 24 h after surgery, we were unable to assess the impact of nefopam on pain beyond this time frame or its potential role in the development of chronic pain. There was a tendency for reduced pain at rest [2 (IQR, 1–4) in the group O *vs.* 1 (IQR, 1–2) in

the group N, median difference –1 (95% CI of –2 to 0), P=0.06], and with coughing [4 (IQR, 3–7) in the group O *vs.* 3 (IQR, 1–4) in the group N, median difference –2 (95% CI of –3 to 0), P=0.03] during the 12–24 h postoperative period. These findings may suggest an analgesic efficacy of nefopam in immediate postoperative period, however extending our study period beyond 24-h would have provided more valuable information. In addition, assessment of the impact of nefopam on quicker rehabilitation or shorter hospital stays would further elucidate its clinical significance regarding the hospitalization process. Lastly, we chose pain score as our primary endpoint to evaluate the efficacy of nefopam as a part of multimodal analgesia. Pain score is a component of patient-reported outcomes. Patient-reported outcomes, such as fatigue, pain, anxiety, can directly measure patient-centered care, and affect the QoR, survival and cancer recurrence (28). However, since our study focused on analgesic effect of nefopam, measurable outcomes such as opioid reduction as our primary endpoint might potentially have yield different outcomes.

Conclusions

In conclusion, administration of 20 mg of nefopam before incision and at the end of surgery relieved postoperative pain at 0 h, 1 h at rest and with coughing after VATS. However, further studies that show sustained analgesic effects beyond 1 h after surgery are warranted to establish nefopam as a multimodal analgesia for VATS.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/rc

Trial Protocol: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/tp

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-30/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC IRB No. 2021-08-068), and registered at ClinicalTrials.gov (NCT05173337) prior to the study participant enrollment. Written informed consent was achieved from all study participants before their study participation.

References

1. Piccioni F, Segat M, Falini S, et al. Enhanced recovery pathways in thoracic surgery from Italian VATS Group: perioperative analgesia protocols. J Thorac Dis 2018;10:S555-63.
2. van der Ploeg APT, Ayez N, Akkersdijk GP, et al. Postoperative pain after lobectomy: robot-assisted, video-assisted and open thoracic surgery. J Robot Surg 2020;14:131-6.
3. Grogan EL, Jones DR. VATS lobectomy is better than open thoracotomy: what is the evidence for short-term outcomes? Thorac Surg Clin 2008;18:249-58.
4. Steinthorsdottir KJ, Wildgaard L, Hansen HJ, et al. Regional analgesia for video-assisted thoracic surgery: a systematic review. Eur J Cardiothorac Surg 2014;45:959-66.
5. Lee J, Lee DH, Kim S. Serratus anterior plane block versus intercostal nerve block for postoperative analgesic effect after video-assisted thoracoscopic lobectomy: A randomized prospective study. Medicine (Baltimore)

2020;99:e22102.
6. Batchelor TJP, Ljungqvist O. A surgical perspective of ERAS guidelines in thoracic surgery. Curr Opin Anaesthesiol 2019;32:17-22.
7. Lee JY, Sim WS, Cho NR, et al. The Antiallodynic Effect of Nefopam on Vincristine-Induced Neuropathy in Mice. J Pain Res 2020;13:323-9.
8. Lim H, Kang S, Kim B, et al. Comparison Between Preoperative and Intraoperative Administration of Nefopam for Acute and Chronic Postoperative Pain in Colon Cancer Patients: A Prospective, Randomized, Double-Blind Study. World J Surg 2019;43:3191-7.
9. Moon JY, Choi SS, Lee SY, et al. The Effect of Nefopam on Postoperative Fentanyl Consumption: A Randomized, Double-blind Study. Korean J Pain 2016;29:110-8.
10. Na HS, Oh AY, Ryu JH, et al. Intraoperative Nefopam Reduces Acute Postoperative Pain after Laparoscopic Gastrectomy: a Prospective, Randomized Study. J Gastrointest Surg 2018;22:771-7.
11. Yeo H, Choi JW, Lee S, et al. The Lack of Analgesic Efficacy of Nefopam after Video-Assisted Thoracoscopic Surgery for Lung Cancer: A Randomized, Single-Blinded, Controlled Trial. J Clin Med 2022;11:4849.
12. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656-9.
13. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology 2013;118:1332-40.
14. Clephas PRD, Hoeks SE, Singh PM, et al. Prognostic factors for chronic post-surgical pain after lung and pleural surgery: a systematic review with meta-analysis, meta-regression and trial sequential analysis. Anaesthesia 2023;78:1005-19.
15. Mehta S, Jen TTH, Hamilton DL. Regional analgesia for acute pain relief after open thoracotomy and video-assisted thoracoscopic surgery. BJA Educ 2023;23:295-303.
16. Shanthanna H, Moisuik P, O'Hare T, et al. Survey of Postoperative Regional Analgesia for Thoracoscopic Surgeries in Canada. J Cardiothorac Vasc Anesth 2018;32:1750-5.
17. Yoon S, Lee HB, Na KJ, et al. Effect of Continuous Infusion of Intravenous Nefopam on Postoperative Opioid Consumption After Video-assisted Thoracic Surgery: A Double-blind Randomized Controlled Trial. Pain Physician 2022;25:491-500.
18. Oh SH, Yoon MH, Lim KJ, et al. Nefopam downregulates autophagy and c-Jun N-terminal kinase activity in the regulation of neuropathic pain development following spinal nerve ligation. BMC Anesthesiol 2018;18:97.
19. Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. Korean J Pain 2014;27:103-11.
20. Jung KT, So KY, Kim SC, et al. Effect of Nefopam-Based Patient-Controlled Analgesia with and without Fentanyl on Postoperative Pain Intensity in Patients Following Laparoscopic Cholecystectomy: A Prospective, Randomized, Controlled, Double-Blind Non-Inferiority Trial. Medicina (Kaunas) 2021;57:316.
21. Zhao T, Shen Z, Sheng S. The efficacy and safety of nefopam for pain relief during laparoscopic cholecystectomy: A meta-analysis. Medicine (Baltimore) 2018;97:e0089.
22. Oh YN, Kim KN, Jeong MA, et al. Effects of nefopam with fentanyl in intravenous patient-controlled analgesia after arthroscopic orthopedic surgery: a prospective double-blind randomized trial. Turk J Med Sci 2018;48:142-9.
23. Girard P, Chauvin M, Verleye M. Nefopam analgesia and its role in multimodal analgesia: A review of preclinical and clinical studies. Clin Exp Pharmacol Physiol 2016;43:3-12.
24. Aymard G, Warot D, Démolis P, et al. Comparative pharmacokinetics and pharmacodynamics of intravenous and oral nefopam in healthy volunteers. Pharmacol Toxicol 2003;92:279-86.
25. Richebé P, Picard W, Rivat C, et al. Effects of nefopam on early postoperative hyperalgesia after cardiac surgery. J Cardiothorac Vasc Anesth 2013;27:427-35.
26. Luo J, Min S. Postoperative pain management in the postanesthesia care unit: an update. J Pain Res 2017;10:2687-98.
27. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12:50-5.
28. Khullar OV, Fernandez FG. Patient-Reported Outcomes in Thoracic Surgery. Thorac Surg Clin 2017;27:279-90.

Cite this article as: Ki HS, Shim JG, Choi HK, Ryu KH, Kang DY, Park J, Ahn JH, Lee SH, Cho EA. Nefopam as a multimodal analgesia in thoracoscopic surgery: a randomized controlled trial. J Thorac Dis 2024;16(6):3644-3654. doi: 10.21037/jtd-24-30