Original Article

Low dose intraoperative ketamine infusion with multilevel paravertebral block for pain after video-assisted thoracic surgery: a randomized-controlled study

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Background: Intraoperative low-dose ketamine infusion has been reported to be an effective adjuvant to opioids for postoperative pain control without major side effects, but it has not been tested in video-assisted thoracic surgery (VATS). The aim of this study was to examine the effect of low-dose intraoperative intravenous ketamine infusion on 24-hour morphine requirement and acute postoperative pain following VATS for lung resection.

Methods: This study was a single center, randomized, double-blind, placebo-controlled study. Thirty-two patients undergoing elective VATS for lung resection in a university hospital were included. Patients were randomly allocated (1:1 ratio) to receive either intraoperative low-dose ketamine (0.2 mg/kg/h) or normal saline infusion starting from intubation to the beginning of chest closure. All patients received multilevel thoracic paravertebral block (TPVB) and morphine was administered postoperatively via the patient-controlled analgesia pump using the same protocol. Time to first analgesia, postoperative cumulative morphine doses at 10, 30 minutes, and the consecutive 1, 2, 6, 12, 18, and 24 hours were recorded. Pain intensity during rest and deep breathing were also assessed by numeric rating scale (NRS) score at 1- and 24-hour postoperatively.

Results: There was no significant difference in median (P_{25}, P_{75}) cumulative 24-hour morphine requirement between the ketamine and the control groups [15 (5.5, 29.5) *vs.* 22.5 (15.3, 40.8) mg, P=0.090]. Patients in ketamine group had significantly longer median pain free time than the control group (27 *vs.* 2 minutes, P=0.006). No difference in overall NRS score at rest or during deep breathing at 1- and 24-hour postoperatively was demonstrated (P=0.861).

Conclusions: Intraoperative low dose ketamine infusion in addition to TPVB does not reduce postoperative morphine consumption or pain intensity but may prolong pain free time in patients undergoing VATS for lung resection.

Keywords: Video-assisted thoracic surgery (VATS); perioperative; acute pain; ketamine; N-methyl-D-aspartate (NMDA) antagonists

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Introduction

Video-assisted thoracic surgery (VATS) is a minimally invasive technique for lung resection which has been shown to reduce postoperative pain and promotes a faster recovery when compared to conventional (open) thoracotomy (1,2). Adequate pain control following thoracic surgery allows early ambulation and recovery, and reduces postoperative pulmonary complications (3,4). Multimodal analgesic techniques, including non-steroidal anti-inflammatory drugs, paracetamol, local infiltration and regional block, have been used over the years in attempt to lessen postoperative pain, as well as minimize opioid consumption and opioid-related side effects (5,6). Still, significant post-thoracotomy pain was reported in 27 to 63 percent after VATS (7,8).

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, was originally introduced as an anesthetic drug. Ketamine has gained growing interests for its analgesic actions at subanesthetic dose and has been extensively studied for its effect on postoperative pain (9,10). However, the results are inconsistent due to the variations in dosing, duration and route of ketamine administration among studies (9,11).

For acute post-thoracotomy pain, results from previous randomized-controlled studies also favored the benefit of perioperative low-dose ketamine in lower pain scores and opioid consumption (12). Most of the studies were performed in open thoracotomy procedures, while published studies of ketamine in VATS are few. Moreover, in spite of heterogeneity in the regimens of administration, ketamine infusion was usually continued during 24–72 hours postoperatively in most studies (9,12). Despite the popularity of postoperative ketamine infusion in the literature, the concerns over the known psychomimetic side effects have limited its generalizability (13). Intraoperative low-dose ketamine infusion has also been reported to be an effective adjuvant to opioids for postoperative pain control without major side effects (14-19), but it has not been tested in VATS. Given that VATS is less invasive than open thoracotomy (2), we hypothesized that intraoperative ketamine might be an adequate adjunct to multilevel thoracic paravertebral block (TPVB) to reduce postoperative pain and opioid consumption after VATS.

The aim of this study was to examine the effect of low-dose intraoperative intravenous ketamine infusion (0.2 mg/kg/h), when combined with multilevel TPVB, on 24-hour morphine requirement and acute postoperative pain following VATS for lung resection. We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/apm-21-766).

Methods

This study was a single center, randomized, double-blind, placebo-controlled study, conducted at Siriraj Hospital, a 2,200-bed quaternary-care medical center located in Bangkok, Thailand. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Siriraj Institutional Review Board (Si 513/2017) and was registered at clinicaltrials.gov (NCT03280017). Patients scheduled for elective VATS for lung resection aged 18–70 years old and capable of using patient-controlled analgesia (PCA) device were included. Exclusion criteria were known hypersensitivity to morphine, ketamine or levobupivacaine, contraindications to or failed TPVBs, body mass index (BMI) >35 kg/m^2, and the likelihood of postoperative mechanical ventilation.

Study groups and intervention

Between October 2017 and December 2018, all patients scheduled for elective VATS were screened for eligibility criteria and enrolled to the study (PL, SW). After informed consents were obtained, participants were randomly allocated (1:1 ratio) to receive either intraoperative low-dose ketamine or normal saline infusion. Randomization was done using computer-generated method by a statistician. Blocks of 4 were used. Randomization sequence was kept separately in opaque sealed envelopes with running numbers (1 to 32).

During the preoperative visits, participants were instructed

about postoperative pain assessment with numeric rating scale (NRS) score and the use of the PCA device. Premedication with analgesics or sedatives were not given before arrival to the operating theater. After placement of standard ASA monitoring, all participants were given 0.2–0.5 mcg/kg of dexmedetomidine infusion in 10 minutes and 0.5 mcg/kg of fentanyl intravenously and then were placed in prone position. Ultrasound-guided multilevel TPVB was performed at the T4 and T5 levels on the side of the operation. The ultrasound transducer was placed in the transverse plane lateral to the designated spinous process. The transverse process, posterior intercostal space, pleura, and paravertebral space were identified. A 4-inch SonoTap (PAJUNK®, Germany) needle was inserted using in-plane technique from lateral to medial plane. Once paravertebral space was reached, 2 mL of normal saline was injected to demonstrate anterior displacement of the pleura. Then, 10 mL of 0.5% levobupivacaine (Abbvie®, UK) was injected into each paravertebral space (total of 20 mL) under ultrasound visualization. All TPVBs were performed by one of the three authors (SS, PL, SP). All participants were assessed for upper and lower levels of blockade using cold swabs at 10 minutes after the TPVBs. Anesthesia was then induced with 1–2 mg/kg propofol, 1 mcg/kg fentanyl and 0.2 mg/kg cisatracurium and maintained with sevoflurane in air/oxygen mixture. Double lumen endobronchial tube was used to establish one-lung ventilation.

After the analgesic levels were confirmed, the envelopes containing the group allocation number were opened, and the study drug was prepared by the anesthesia personnel not involving in the study or patient care. Racemic ketamine (Hameln, Germany) was prepared in normal saline to 50 mg in 50-mL syringe (1 mg/mL) for patients in the ketamine group. Normal saline was also prepared in the 50-mL syringe identical to ketamine for patients in the control group. Each syringe was labelled as 'study drug'. Participants received study drugs according to their group allocation. Study drug was infused at the rate of 0.2 mL/kg/h starting immediately after double-lumen endobronchial tube was placed and continued throughout the intraoperative period. The study drug infusion was discontinued at the beginning of chest closure. The participants, as well as, the anesthesiologists involving in providing paravertebral blocks and intraoperative cares were blinded to group allocation.

During the intraoperative period, fentanyl 0.5–1 mcg/kg boluses were given if the systolic blood pressure was elevated more than 20% from baseline. End-tidal sevoflurane concentration was maintained at 0.8–1 age-adjusted minimal alveolar concentration. Hypotension was defined as a 20% reduction in systolic blood pressure from baseline and was treated with a bolus of 6 mg of ephedrine and/or 4 mcg of norepinephrine. All participants were extubated at the end of surgery and transferred to the post anesthesia care unit (PACU). Intravenous PCA device (Sapphire™, ICU Medical, Inc., US) was provided from PACU arrival until the 24th hour after surgery. Morphine was administered via the PCA pump using the same protocol for all patients (bolus 1 mg, lockout interval 5 minutes, 4-hour limit 30 mg).

Outcomes

The primary outcome of the study was 24-hour cumulative morphine dosage. Time from the end of the surgery to the time of first PCA device triggering was obtained from PCA device logs. Postoperative cumulative morphine doses at 10, 30 minutes, and the consecutive 1, 2, 6, 12, 18, and 24 hours were also recorded.

Pain intensity during rest and deep breathing were assessed using NRS score 0–10 (0= no pain, 10= worse pain) at 1- hour and 24-hour postoperatively. The peak expiratory flow rates (PFR) were measured using a portable peak flow meter (MicroPeak®, CareFusion, USA) during the preoperative visits, and at 24-hour after surgery. The percentage difference between preoperative and postoperative PFR was calculated as [(preoperative PFR – postoperative PFR)/preoperative PFR] ×100. Occurrence of nausea and vomiting (PONV), hallucinations, nightmares, delirium and requirement for antiemetic therapy were also recorded. All outcome accessors were also blinded to group allocation.

Statistical analysis

Sample size was calculated based on a previous study by Kaya *et al*. (20), which demonstrated a 24-hour cumulative morphine consumption of 32±5 mg (mean ± SD) after VATS in patients receiving multilevel TPVB using 20 mL of 0.5% bupivacaine. A 20% reduction in the 24-hour cumulative morphine consumption anticipated in the ketamine group compared with the normal saline group (control) was hypothesized. Using 2-sided type I error of 0.05 and 90% power, a sample of 16 participants per group was required. Query Advisor 3.0 (Statistical Solutions Ltd, Cork, Ireland) was used for sample size estimation. Data

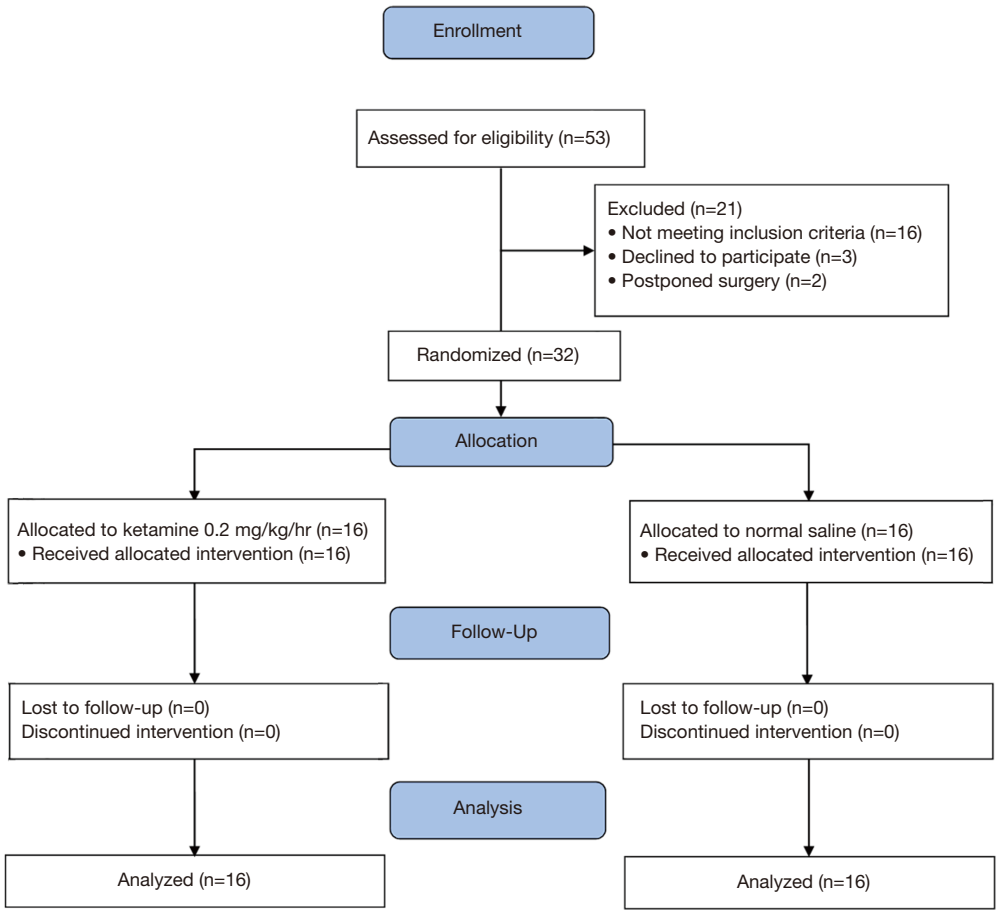

Figure 1 CONSORT flow diagram.

were processed using SPSS Statistics for Windows version 18 (SPSS Inc., Chicago, Ill, USA). Continuous data such as age, BMI, duration of surgery, duration of anesthesia, drug doses, percentage difference between preoperative and postoperative PFR, NRS score and 24-hour morphine consumption are presented as mean ± SD or median (P_{25}, P_{75}). Demographic and perioperative data were compared using Student's *t*-test or Mann-Whitney U test. NRS score and 24-hour morphine consumption were compared using Repeated Measurement ANOVA. Time to first PCA-triggering was analyzed using survival analysis and generalized Wilcoxon's test for comparison of 2 survival curves. Categorical data such as gender and incidence of side effects are presented as number (%) and compared using χ^2 test. A P value less than 0.05 was considered statistically significant.

Results

From October 2017 to December 2018, 32 participants were enrolled (16 participants in each group) and completed the study (*Figure 1*). Mean age was 55.8±10.8 years and 68.8% were female. There were no significant differences in patient demographic data between the two groups (*Table 1*). Despite randomization, 13 (81.3%) patients in the control group underwent lobectomy/segmentectomy, and only 6 (37.5%) patients in the ketamine group had the same procedure (P=0.012). Moreover, the duration of surgery was significantly longer in the control group compared to the ketamine group (153.6±67.0 *vs.* 95.3±51.0 minutes, P=0.009). The total intraoperative ketamine dose administered was 0.34±0.15 mg/kg in the ketamine group. There were no differences in intraoperative dexmedetomidine and fentanyl doses (*Table 2*). Successful TPVB was achieved in

Table 1 Baseline patient characteristics

Variables	Ketamine (n=16)	Normal saline (n=16)
Age (years)	53.5±11.9	58.0±9.4
Weight (kg)	62.3±12.6	63.2±12.8
Height (cm)	161.5±8.1	157.5±6.9
BMI (kg/m^2)	23.8±4.3	25.4±4.1
Female	10 (62.5)	12 (75.0)

Values are presented as mean ± standard deviation or number of patients (%). BMI, body mass index.

Table 2 Perioperative characteristics

Variables	Ketamine (n=16)	Normal saline (n=16)	P value
Types of surgery			0.012
Lobectomy/segmentectomy	6 (37.5)	13 (81.3)	
Wedge resection	10 (62.5)	3 (18.7)	
Duration of anesthetic (min)	160.6±53.1	215.9±71.3	0.019
Duration of surgery (min)	95.3±51.0	153.6±67.0	0.009
Intraoperative amount of the study drug (mL)	21.1 ±10.6	34.1±17.3	0.017
Intraoperative dexmedetomidine (mcg)	29.2±5.8	30.0±6.7	0.717
Intraoperative fentanyl (mcg)	71.5±20.1	77.4±34.7	0.560
Postoperative 24-hours morphine consumption (mg)	15.0 (5.5, 29.5)	22.5 (15.3, 40.8)	0.090
Difference between preoperative and 24-hour postoperative PFR (%)	34.9±16.0	51.8±15.2	0.007
Antiemetic therapy	8 (50.0)	10 (62.5)	0.722

Values are presented as mean ± standard deviation, median (P_{25}, P_{75}) or number of patients (%). Difference between preoperative and 24-hour postoperative peak flow rate (PFR) = [(preoperative PFR – postoperative PFR)/preoperative PFR] ×100 (%).

all patients. Analgesic levels after paravertebral blocks were shown in *Figure 2*.

There was no significant difference in the median (P_{25}, P_{75}) cumulative 24-hour morphine consumption between the ketamine [15 (5.5, 29.5) mg and the control group 22.5 (15.3, 40.8) mg, P=0.090] (*Figure 3*), however, longer median pain free time was observed in the ketamine group at 27 minutes compared to 2 minutes in the control group (P=0.006) (*Figure 4*). No difference in postoperative NRS score at 1- and 24-hour at rest and during deep breathing was observed (P=0.861) (*Figure 5*). The control group had higher percentage difference between preoperative and postoperative PFR than the ketamine group (51.8%±15.2% *vs*. 34.9%±16.0%, P=0.007). There was no difference in antiemetic use and none of the participants reported postoperative nightmares, hallucinations or delirium.

Discussion

The main finding from this study is that, in patients undergoing VATS for lung resection with single shot multilevel TPVB, intraoperative low dose ketamine infusion does not reduce 24-hour morphine consumption, and postoperative NRS score at rest and movement compared to placebo, however, it prolongs the time to first analgesic requirement.

Several studies have investigated the efficacy of intravenous ketamine on acute postoperative thoracotomy pain (12,19,21-25). There is no consensus in standard dose, timing and route of administration of ketamine among studies (12). A systematic review of perioperative ketamine used for thoracotomy pain by Moyse *et al*., which included 15 randomized control trials, reported a significant reduction in acute postoperative pain.

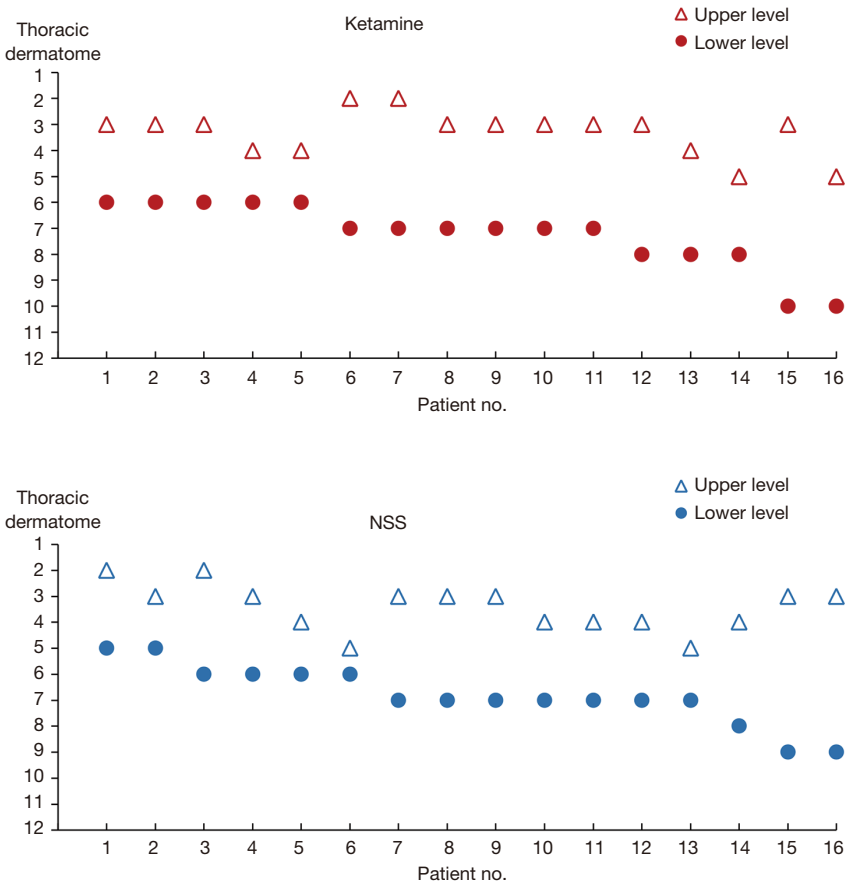

Figure 2 Spreading of levels of sensory blockade in ketamine group (upper panel) and normal saline group (lower panel) at 10 minutes after single shot multilevel thoracic paravertebral block.

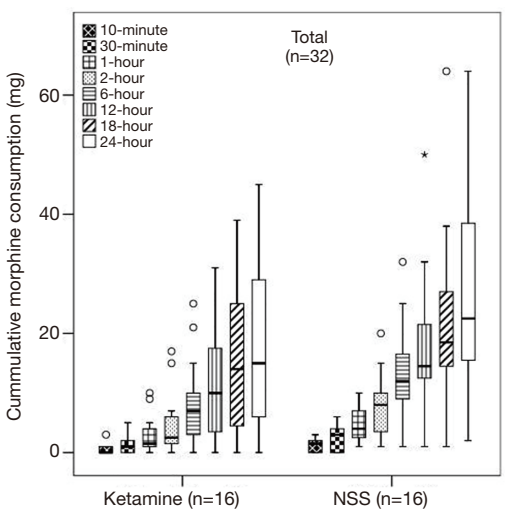

Figure 3 Median boxplot (P_{25}, P_{75}) with bars showing the cumulative morphine consumption during the first 24 hours postoperatively (P=0.090).

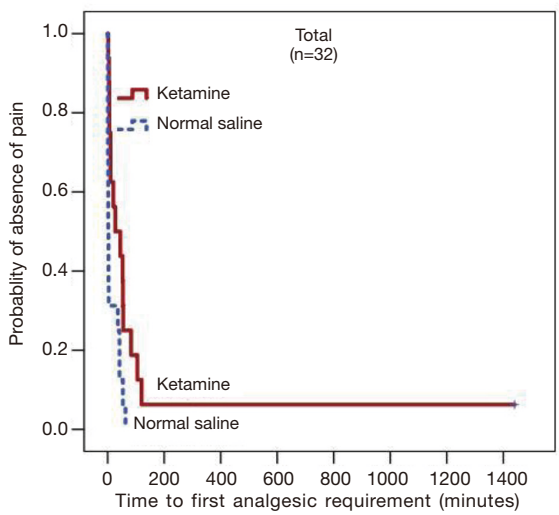

Figure 4 Kaplan-Meier survival curve of time to first trigger of patient-controlled analgesia (PCA) machine in the ketamine and the control groups (P=0.006).

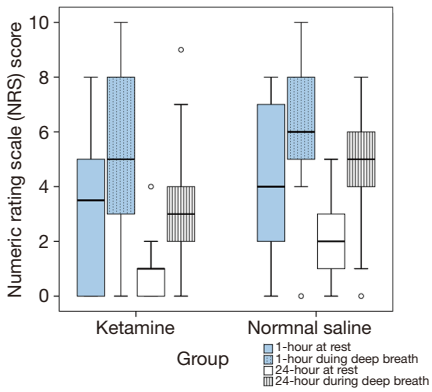

Figure 5 Median boxplot (P_{25}, P_{75}) with bars showing the median and the 10th and 90th percentiles and open circles showing the extremes of numeric rating scale (NRS) score at 1- and 24-hour postoperative at rest and during deep breath (P=0.861).

Among the 15 studies, ketamine was given intravenously via infusion or IV PCA in 11 studies and positive results were demonstrated in 7 studies (470 participants) (12). Although different regimens were used, in all positive studies, ketamine was continued to 48–72 hours postoperatively (19,23,26-30). The authors concluded that ketamine was effective in attenuating acute post-thoracotomy pain (12). To our knowledge, our study is among the first studies to examine analgesic effects of intraoperative low-dose ketamine in VATS for lung resection.

Intraoperative bolus and/or infusion of low-dose ketamine was assessed in several studies (9,11). Despite some inconsistency, an opioid-sparing effect of intraoperative low-dose ketamine has been demonstrated after abdominal (15,18,31), orthopedics (32-34) and gynecologic procedures (35). However, for thoracotomy procedures, only one study (40 patients) had compared preincisional ketamine bolus (0.5 mg/kg) and placebo which the authors reported no difference in pain scores or opioid consumption (24). Due to concerns related to the dose-related side effects of ketamine, such as dysphoria and hallucination, we used low-dose intraoperative ketamine infusion which was discontinued at the end of the procedure. At sub-anesthetic dose (<0.3 mg/kg), the psychomimetic risk is believed to be insignificant (36,37). Moreover, intraoperative infusion is relatively simple and require less nursing care postoperatively at wards. Since the dose and mode of delivery varied greatly among the literatures, we have chosen the practical dose suggested by Gorlin *et al.*, (0.1–0.3 mg/kg followed by 0.1–0.2 mg/kg/hour infusion) (36). Recent studies have demonstrated that single bolus dose of ketamine may be inefficient for postoperative pain (38,39) and continuous intraoperative infusion was recommended (40). We also determined to specifically evaluate whether the intraoperative 'infusion only' regimen would yield the same effect when subanesthetic ketamine was combined with multilevel TPVB. Our hypothesis was that VATS resulted in less pain and tissue injury compared to open thoracotomy, therefore, we aimed to examine the effect of low-dose intraoperative ketamine rather than postoperative ketamine infusion. As a result, intraoperative infusion of 0.2 mg/kg/hour of ketamine was adopted.

In our study, we could not demonstrate the difference in 24-hour morphine consumption and postoperative pain between the intraoperative low-dose ketamine and the control groups. The negative results may be explained by several reasons. First, it is possible that the dose of intraoperative ketamine was inadequate. The dose of intraoperative ketamine used in our study was only 0.2 mg/kg/hour, which was relatively low to avoid possible side effects. In a dose-finding study by Suzuki *et al*. (23), the minimal effective plasma concentration that reduced postoperative pain was 20 ng/mL when ketamine was administered via thoracic epidurals. The reported doses of intravenous infusion of ketamine in previous studies, which demonstrated analgesic benefit, varied between 0.05–0.5 mg/hour (9,10). Most studies also started with a bolus dose of 0.15–0.5 mg/kg (9,10), in which, absence in our study. The mean duration of the surgery for the ketamine group in our study was only 95.3±51.0 min resulting in small cumulative doses of ketamine, while the duration of surgery ranged between 2–4.6 hours in the other studies with positive results (15-17). Although ketamine is believed to have central desensitization effect after low dose administration due to its high affinity to NMDA receptors (36,41), the mean cumulative dose of ketamine given for each patient in our study was only 21.1±10.6 mg and may not reach effective plasma concentration (20–150 ng/mL) (40). Given that ketamine bolus was not utilized in our study, it is possible that sufficient plasma concentration was not achieved, especially, when the duration of surgery was short.

Secondly, TPVB may have already reduced 24-hour opioid requirement; hence, ketamine may not have provided additional analgesic benefit. Results from previous studies have confirmed the effectiveness of TPVB in acute post-thoracotomy pain control (42,43). Borys *et al*. compared between TPVB and preemptive bolus ketamine

in patients undergoing posterolateral thoracotomies and reported that TPVB was superior to ketamine in reducing pain intensity and morphine consumption (44). Ketamine has only moderate effect on acute postoperative pain (36,40), therefore, its advantage is less likely to be shown when combined with other multimodal analgesia techniques (25,45,46). In a study by Joseph *et al*., no difference in pain was reported in patients after open thoracotomy when higher dose of ketamine infusion for 48 hours was used in combination with thoracic epidural compared with placebo (22). Another study in thoracotomy patients by Yazigi *et al*. also could not demonstrate the difference in pain between ketamine infusion and placebo when multimodal analgesic techniques (intercostal nerve block, paracetamol and ibuprofen) were used in both groups (25). Moreover, all patients in our study were sedated with dexmedetomidine during TPVB. Dexmedetomidine is an alpha-2 adrenergic receptor agonist, which provides dose-dependent analgesia (47). Dexmedetomidine has been demonstrated as an effective adjuvant to opioids for postoperative pain after thoracic surgery (47-49). Although the doses administered in our study was low, intraoperative dexmedetomidine may have also decreased the postoperative pain, especially upon arrival at the PACU (50). Since VATS is associated with lower postoperative pain compared to traditional open thoracotomy (2,51), when pain is partially suppressed with TPVB and dexmedetomidine, the benefit of adjunct ketamine may be subtle.

Furthermore, there were two categories of surgical procedures included in the present study; (I) lobectomy and segmentectomy, and (II) wedge resection. Most participants who underwent lobectomy were unintentionally randomized into the control group, whereas, most participants who underwent wedge resection were in ketamine group. Because VATS lobectomy is associated with longer duration and more extensive surgical approach compared to VATS wedge resection (52), subsequently, more intense postoperative pain is often observed (53). This may result in uneven postoperative pain intensity between the two groups, thus, a confounder in our study.

In our study, the patients in ketamine group had significantly less percent reduction of the 24-hour postoperative PFR from baseline compared to the control group. During early postoperative period, substantial impairment in the pulmonary function is frequently observed as a result of reduced lung volume, decreased lung compliance, respiratory muscles and diaphragmatic dysfunction after lung resection (54,55). Low dose ketamine may have a protective effect on postoperative pulmonary function by stimulating respiration and offset opioid-induced respiratory depression (56-58). As an NMDA receptor antagonist, ketamine can attenuate central sensitization and results in lower opioid requirement in order to achieve the same analgesia, thus, reducing the undesirable side effects (59). Ketamine also has bronchodilator effect and its sympathomimetic activity is known to relieve airways spasm (60). Michelet *et al*. demonstrated better postoperative pulmonary function after lobectomy in patients receiving ketamine with morphine (1:1) via PCA when compared to PCA morphine alone on the first postoperative day (61). In their study, significant lower morphine consumption was demonstrated only after 36th hour following surgery and no difference in pain scores were reported during the first day. However, in our study, the benefit of ketamine on the postoperative PFR changes may have been confounded by the disproportion of the procedure types (lobectomy versus wedge resection). The higher proportion of patients underwent wedge resection in the ketamine group can result in less complicated surgery, shorter duration of anesthesia, and a more substantial lung volume preserved. Furthermore, ketamine infusion was not extended through the postoperative period and neither reduction in pain nor opioid requirement could be demonstrated. Further studies using larger sample size with lobectomy procedures and continuous postoperative infusion for longer period are required to conclude the effects of ketamine on postoperative pain and pulmonary function.

There are limitations to this study. First, although our study was an RCT, discrepancies in perioperative characteristics were observed, which could be regarded as potential confounders. In our institution, VATS has mostly replaced conventional thoracotomy in the treatment of most lung pathologies, which results in the variety of procedural complexity and patient characteristics. Second, the small sample size had led to limitation for subgroup analysis to eliminate the confounders. Third, we did not give a bolus dose of ketamine before starting the infusion, therefore, the effective plasma concentration may have not reached in the shorter procedures. Finally, the use of nonsteroidal anti-inflammatory drugs, COX-inhibitors and paracetamol was omitted during the study period with the intention to emphasize the effects of ketamine, hence, this may not resemble routine practice.

In conclusion, intraoperative low dose ketamine infusion in addition to TPVB does not reduce postoperative

morphine consumption or pain intensity but may prolong the pain free time in patients undergoing VATS for lung resection. The reduction in morphine consumption might be more pronounced using higher dose of ketamine or in more invasive VATS procedures.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-766

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-766

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-766). 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). The study protocol was approved by the Siriraj Institutional Review Board (Si 513/2017). Written informed consent was obtained from all participants.

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