UC Davis

UC Davis Previously Published Works

Title

Effects of perioperative esketamine infusion on chronic pain after video-assisted thoracoscopic lung resection: a multicentre, randomised, double-blind clinical trial

Permalink

https://escholarship.org/uc/item/8nq691md

Journal

British Journal of Anaesthesia

ISSN

0007-0912

Authors

Wang, Qin-Yun

Zhang, Jian-You

Gu, Jia-Qi

et al.

Publication Date

2026-10-01

DOI

10.1016/j.bja.2026.08.039

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2026.08.039
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Effects of perioperative esketamine infusion on chronic pain after video-assisted thoracoscopic lung resection: a multicentre, randomised, double-blind clinical trial

Qin-yun Wang[1,2,†], Jian-you Zhang[3,†], Jia-qi Gu[4,†], Bin Li[5], Yong-tao Gao[6], Fei Guo[7], Yu Qi[8], Qian Li[9], Heng-fei Luan[10], Ju Gao[11], Hong Liu[12], Ke Peng[1,2], Xi-sheng Shan[1,2,*], Yi-shan Lei[1,2,*] and Fu-hai Ji[1,2,*]

[1]Department of Anaesthesiology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China, [2]Institute of Anaesthesiology, Soochow University, Suzhou, Jiangsu, China, [3]Department of Anaesthesiology, Affiliated Hospital of Yangzhou University, Yangzhou, Jiangsu, China, [4]Department of Anaesthesiology, Suzhou Municipal Hospital, Suzhou, Jiangsu, China, [5]Department of Anaesthesiology, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China, [6]Department of Anaesthesiology, Affiliated Hospital of Nantong University, Nantong, Jiangsu, China, [7]Department of Anaesthesiology, Nantong First People's Hospital, Nantong, Jiangsu, China, [8]Department of Anaesthesiology, Xuzhou Central Hospital, Xuzhou, Jiangsu, China, [9]Department of Anaesthesiology, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China, [10]Department of Anaesthesiology, The First People's Hospital of Lianyungang, Lianyungang, Jiangsu, China, [11]Department of Anaesthesiology, Northern Jiangsu People's Hospital, Yangzhou, Jiangsu, China and [12]Department of Anesthesiology and Pain Medicine, University of California Davis Health, Sacramento, CA, USA

*Corresponding authors. E-mails: xisheng83@sina.com, lysmed@163.com, jifuhaisuda@163.com
[†]contributed equally to this work.

Abstract

Background: Chronic postsurgical pain after thoracoscopic surgery remains common. We investigated whether perioperative low-dose esketamine infusion would reduce chronic pain after video-assisted thoracoscopic lung resection.

Methods: In this multicentre, randomised controlled trial, 914 adults were randomly assigned (1:1) to receive either esketamine or normal saline. Esketamine was administered as a 0.1 mg kg^{-1} bolus at induction, followed by continuous intraoperative infusion (0.1 mg kg^{-1} h^{-1}) and postoperative infusion (0.015 mg kg^{-1} h^{-1}) for 48 h. The primary outcome was chronic pain at 3 months, defined as persistent pain with a numeric rating scale score ≥1 during coughing in the surgical region. Secondary outcomes included postoperative pain, supplemental analgesics use, recovery of bowel function, in-hospital adverse events, and esketamine-related side-effects.

Results: We analysed 873 patients (median age, 55 yr; 63% female). The incidence of 3 month chronic pain was lower in the esketamine group than in the control group (14.7% *vs* 21.2%; adjusted odds ratio, 0.62; 95% confidence interval, 0.43–0.90; P=0.013). A reduction was also observed when using a *post hoc* outcome definition of a numeric rating scale pain score ≥3 during coughing at 3 months (adjusted odds ratio, 0.39; 95% confidence interval, 0.19–0.84; P=0.015). Esketamine also reduced overall pain scores at rest and during coughing within the first 48 h, and decreased supplemental analgesic requirements within 48 h and 3 months.

Conclusions: Perioperative low-dose esketamine infusion significantly reduced 3 month chronic pain after thoracoscopic lung resection without increasing adverse effects.

Received: 22 February 2026; **Accepted:** 21 August 2026

© 2026 British Journal of Anaesthesia. Published by Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.
For Permissions, please email: permissions@elsevier.com

Clinical trial registration: ChiCTR2000040012.
Trial registration: This trial was registered on the Chinese Clinical Trial Registry (Identifier: ChiCTR2000040012; principal investigator: Fu-hai Ji; dated November 18, 2020; https://www.chictr.org.cn/showprojEN.html?proj=62319).

Keywords: chronic postsurgical pain; esketamine; lung resection; multimodal analgesia; video-assisted thoracoscopic surgery

Editor's key points

- Prior studies on esketamine, a potent N-methyl-D-aspartate receptor antagonist, for preventing chronic postsurgical pain have shown inconsistent results due to heterogeneous protocols and small sample sizes.
- In this multicentre, randomised, double-blind trial, the authors show that low-dose esketamine infusion significantly reduces the incidence of chronic postsurgical pain on coughing and the need for supplementary analgesics 3 months after video-assisted thoracoscopic surgery (VATS) lung resection, without increasing the risk of adverse effects.
- This suggests the relevance of including perioperative low-dose esketamine infusion in multimodal analgesic strategies for VATS.
- Whether these results also apply to other surgical models and longer time outcomes after surgery remains to be determined.

Minimally invasive approaches, particularly video-assisted thoracoscopic surgery (VATS), have become the prevalent technique for lung resection, providing the advantages of reduced surgical trauma and accelerated recovery compared with open thoracotomy.[1–3] Despite these benefits, the incidence of chronic postsurgical pain (CPSP) after thoracoscopic surgery remains substantial, with reported rates ranging from 22% to 63%.[4] CPSP is associated with impaired long-term postoperative outcome and diminished quality of life.[5] CPSP is a complex and multifactorial condition involving both biological and psychological mechanisms, and it frequently presents with neuropathic features that are poorly responsive to opioids.[6]

Esketamine, the dextrorotatory isomer of ketamine, is a potent N-methyl-D-aspartate (NMDA) receptor antagonist with approximately twice the analgesic potency of ketamine, additional antidepressant effects, and a lower incidence of psychotomimetic adverse reactions.[7,8] It has been proposed as a component of multimodal analgesia for treatment of acute postoperative pain.[10] Nonetheless, clinical investigations of esketamine for the prevention of CPSP have yielded inconsistent findings. Yan and colleagues[11] demonstrated that substituting opioids with esketamine—administered intraoperatively via i.v. injection and epidural infusion, and continued after surgery as an epidural infusion—significantly reduced the incidence of mild CPSP in patients undergoing VATS. In contrast, another study found that a single preoperative dose of esketamine had no significant impact on the CPSP incidence or postoperative analgesic consumption.[12] These discrepancies derived from heterogeneous protocols and relatively small sample sizes highlight the need for a multicentre trial to evaluate the effect of esketamine on CPSP after thoracoscopic surgery.

Accordingly, we conducted a multicentre, randomised, double-blind clinical trial to evaluate whether perioperative esketamine administration could reduce the incidence of CPSP in patients undergoing VATS lung resection. We hypothesised that perioperative low-dose esketamine infusion would lower the risk of developing CPSP.

Methods

Trial design

This investigator-initiated, multicentre, randomised, double-blind, controlled clinical trial was conducted at 10 tertiary hospitals in China. The study protocol was approved by the clinical research ethics committees of all participating institutions, and was prospectively registered with the Chinese Clinical Trial Registry on November 18, 2020, before the enrolment of the first participant. All participants provided written informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) guidelines,[13] and was overseen by an independent data safety and monitoring committee (DSMC). The complete study protocol has been published,[14] and is available in Supplementary File 1.

Participants

Eligible participants were adults aged 18 to 65 yr with an ASA physical status of 1–3 undergoing elective VATS lung resection under general anaesthesia and expected to remain hospitalised for at least 48 h after surgery. Exclusion criteria included known allergy to study medications; contraindications to nonsteroidal anti-inflammatory drugs, including chronic kidney disease and renal failure (based on creatinine levels and creatinine clearance); psychiatric disorders; history of chronic pain; communication difficulties; emergency or trauma cases; history of intraoperative awareness; planned postoperative transfer to intensive care unit; or unwillingness to use patient-controlled i.v. analgesia (PCIA).

Randomisation and blinding

Patients were randomised in a 1:1 ratio to receive either esketamine or normal saline (control) using a block size of 4, stratified by study centre. Randomisation was centrally implemented through a secure web-based system (http://random.91trial.com). Allocation concealment was maintained by a research coordinator who prepared identical, opaque, sealed envelopes. Approximately 30 min before

anaesthesia, an independent research nurse opened the assigned envelope and prepared the study medication in identical syringes and devices labelled only with the patient identification number. Patients, surgeons, anaesthesiologists, and postoperative outcome assessors were blinded to treatment allocation throughout the study.

Anaesthesia, intervention, and multimodal analgesia

Anaesthesia was induced with midazolam (1–3 mg), propofol (2–2.5 mg kg^{-1}), sufentanil (0.3–0.6 μg kg^{-1}), and cisatracurium (0.2 mg kg^{-1}), followed by tracheal intubation with a double-lumen endobronchial tube to facilitate one-lung ventilation. Anaesthesia was maintained with either inhaled sevoflurane or continuous propofol infusion, titrated to achieve a bispectral index of 40–60. If heart rate or blood pressure increased by ≥20% above baseline, intraoperative analgesia was supplemented with sufentanil (0.1–0.2 μg kg^{-1}).[15] Before skin incision, local anaesthesia with 5 ml of ropivacaine 0.375% was administered at each planned incision site. When thoracic drainage was placed, an additional 5 ml of ropivacaine 0.375% was infiltrated around the drainage tube incision. All patients were managed in accordance with a standardised enhanced recovery after surgery protocol,[1] with detailed anaesthesia procedures provided in eMethods in Supplementary File 2.

In the esketamine group, patients received an i.v. esketamine bolus (0.1 mg kg^{-1}) after induction, followed by a continuous infusion (0.1 mg kg^{-1} h^{-1}) until the end of the surgery. After surgery, PCIA was administered for 48 h using a solution of sufentanil (2 μg kg^{-1}) and esketamine (1 mg kg^{-1}) in 100 ml saline. The pump was programmed for a background infusion of 1.5 ml h^{-1} (equivalent to 0.015 mg kg^{-1} h^{-1} of esketamine), a bolus dose of 2 ml, and a 10 min lockout. In the control group, patients received volume-matched saline both as a bolus after induction and as a continuous infusion intraoperatively. After surgery, PCIA was provided for 48 h with sufentanil (2 μg kg^{-1}) in 100 ml saline, using identical pump settings.

Patients were instructed to self-administer sufentanil via PCIA when their visual analogue scale (VAS) pain score was ≥4 (0=no pain, 10=worst pain). As part of multimodal analgesia, all patients received flurbiprofen axetil 50 mg i.v. at the beginning and end of the surgery, followed by 50 mg administered twice daily on postoperative days 1 and 2. If pain remained uncontrolled (VAS ≥6), i.v. supplemental analgesic (morphine, fentanyl, oxycodone, or tramadol) was administered. At 48 h after surgery, patients were generally transitioned from i.v. analgesia to oral tramadol or, when indicated, stronger oral opioids (e.g. oxycodone), followed by stepwise de-escalation to non-opioid analgesics (e.g. acetaminophen). Perioperative analgesia management was standardised across all study centres.

Data collection and measurement

Pain intensity at rest and during coughing was assessed using the VAS at 1, 4, 8, 24, and 48 h after surgery. Upon discharge, each patient was provided with a numeric rating scale (NRS) chart, and pain intensity was assessed using the standardised question: 'Over the past 24 h, how would you rate the pain in your operated chest on a scale from 0 to 10 on coughing?' NRS pain scores were evaluated via telephone follow-up at 7 days, 1 month, and 3 months after surgery, with additional pain characteristics recorded at 1 and 3 months.

Time to first flatus was recorded as an indicator of postoperative recovery of bowel function.[16] Neuropathic pain at 3 months was evaluated via telephone using the symptom-based seven-item Douleur Neuropathique 4 (DN4) questionnaire, which assesses three pain characteristics (burning, painful cold, and electric shocks) and four associated symptoms (tingling, pins and needles, numbness, and itching). Each positive item was scored 1 point, yielding a total score ranging from 0 to 7; a score of ≥3 was considered indicative of neuropathic pain (Supplementary File 2, eTable 1).[17] Delirium assessment was conducted twice daily (06:00–09:00 and 16:00–19:00) during the first three postoperative days by trained physicians using the 3-Minute Diagnostic Confusion Assessment Method, and sleep quality during the preceding night was additionally evaluated at the morning assessment.[18] Research staff conducting outcome assessments were blinded to treatment allocation.

Study outcomes

The primary outcome was the incidence of CPSP at 3 months, defined as persistent pain with an NRS score ≥1 during coughing in the surgical region.[19,20] Secondary outcomes included VAS pain score at rest and during coughing at 1, 4, 8, 24, and 48 h, and NRS pain scores during coughing at 7 days and 1 month after surgery; the requirement for supplemental analgesics within 48 h and 3 months; time to recovery of bowel function; in-hospital adverse events (hypoxaemia, hypotension, nausea and vomiting, and itching); and esketamine-related side-effects, including dreaminess, nightmares, hallucination, delirium, restlessness, orientation difficulty, laryngospasm, blurred vision, tachycardia, and salivation. Exploratory outcomes included opioid consumption from PCIA, total opioid consumption within 48 h, intraoperative awareness, delayed recovery, stroke, pulmonary infection, incision infection, sleepiness, length of postoperative hospital stay, neuropathic pain at 3 months, and pain characteristics at 1 and 3 months after surgery. All opioid consumption (i.v. and oral) was converted to i.v. morphine milligram equivalents (MMEs) using the Equivalent Opioid Calculator (https://clincalc.com/Opioids/). Moderate-to-severe chronic pain was defined as an NRS pain score ≥3, which is generally considered clinically meaningful and likely to interfere with daily activities.[21,22] Adverse events and postoperative complications were monitored throughout hospitalisation.

Statistical analysis

According to previous studies, the incidence of chronic pain after VATS may be as high as 50%.[23] We hypothesised that esketamine administration would reduce this incidence by 20%.[24] The study was powered to detect this difference at a two-sided significance level of 0.05 and 80% power, while accounting for an anticipated dropout rate of 15%. The required sample size was calculated to be 914 patients, with 457 patients assigned to each group.

Continuous variables were summarised as means (standard deviations [SD]) or medians (interquartile ranges) according to data distribution, and categorical variables as counts (percentages). Standardised differences were used to assess the baseline and perioperative imbalance, with

standardised differences >0.2 indicating meaningful imbalance. For outcomes, categorical variables were compared using the χ^2 test or Fisher's exact test, while continuous variables were compared using the unpaired *t*-test or Mann–Whitney *U*-test as appropriate. Treatment effects were reported as odds ratios (ORs) or median differences with 95% confidence intervals (CIs), estimated using the Baptista–Pike or Hodges–Lehmann methods, respectively. Binary outcomes were further analysed using mixed-effects logistic regression models, and continuous outcomes using mixed-effects linear regression models, with recruitment site included as a random effect. Treatment effects were presented as adjusted ORs or adjusted mean differences with 95% CIs. For VAS pain scores measured repeatedly during the first 48 h after surgery, a linear mixed-effects model was fitted, with time modelled quadratically. An autoregressive (AR[1]) variance–covariance structure was specified at the patient level to account for within-patient correlations among repeated measurements. Patient identification and recruitment site were included as random intercepts. The estimated marginal mean difference between groups, averaged across all repeated time points, was used to assess the overall between-group difference in pain scores over the 48 h periods. Time to recovery of bowel function was analysed using a Cox proportional-hazards model with recruitment site as a random effect. The event was defined as recovery of bowel function within 48 h after surgery. Treatment effects are reported as hazard ratios (HRs) with 95% CIs.

The primary outcome was analysed according to the modified intention-to-treat approach, including all randomised patients who underwent surgery and had data available for the primary outcome. The per-protocol analysis excluded patients with major protocol violations, including non-adherence to the planned postoperative analgesic protocols, reoperation, or any other surgical procedure within the 3 month postoperative period. Sensitivity analysis for missing primary outcome data was performed using multiple imputation by chained equations (m=5), with estimates pooled using Rubin's rules. For each imputed data set, we further fitted a mixed-effects logistic regression model including recruitment site as a random effect. Predefined subgroup analyses of the primary outcome were performed according to trial sites, sex, BMI, diabetes mellitus, surgical type, and number of ports. Secondary outcomes were not adjusted for multiple comparisons and should be interpreted with caution. Additional *post hoc* analyses included: (1) NRS pain scores ≥3 at rest and during coughing at 3 months after surgery; and (2) the total DN4 interview score analysed as a continuous variable. These analyses were performed using mixed-effects logistic or linear regression models, with age, sex, type of surgery, and number of ports included as fixed effects and recruitment site as a random effect.

After enrolment of half of the planned sample size, a prespecified interim analysis incorporating the O'Brien–Fleming boundary, conditional power assessment, and safety data was conducted by an independent statistician. The interim report was reviewed by the DSMC, which determined whether the trial should proceed or be terminated earlier. For the study outcome, statistical significance was defined as P<0.05. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) or R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) by independent statisticians.

Results

Study flow

From April 1, 2021, to October 31, 2025, 1126 participants were screened for eligibility (Fig. 1). After exclusion of 212 participants, 914 were randomised. Twelve patients in the esketamine group and 10 in the control group had surgery delayed or cancelled after randomisation, while 10 patients in the esketamine group and nine patients in the control group withdrew consent before surgery. At 3 months, 21 patients in the esketamine group and 22 in the control group were lost to follow-up (Supplementary File 2, eTable 2). The modified intention-to-treat analysis included 414 patients in the esketamine group and 416 in the control group. The per-protocol analysis excluded 17 patients: one because of reoperation, and 16 because of deviations from the postoperative analgesia protocol (six did not receive patient-controlled analgesia, eight discontinued it prematurely, and two received PCIA prepared with non-protocol-specified doses) (Supplementary File 2, eTable 3). At the prespecified interim analysis, the O'Brien–Fleming stopping boundary was not crossed, and the trial continued as planned (Supplementary File 2, eResults).

Baseline and perioperative data

Baseline characteristics were well balanced between groups (Table 1). The median (interquartile range) age was 55 (47–60) yr, with 549 patients (63%) being female. The mean (SD) BMI was 23.2 (2.6) kg m^{-2}. Most patients were classified as ASA physical status 1 or 2. A history of thoracic surgery was reported in 1.8% of patients, and 2.7% had a history of malignancy.

Heart rate and mean arterial pressure were generally comparable between the two groups (Table 2). The proportions of patients receiving total i.v. anaesthesia and sevoflurane were similar between the groups. Of the 873 patients, 156 (17.9%) underwent wedge resection, 252 (28.9%) segmentectomy, and 465 (53.3%) lobectomy. Among these procedures, 409 (46.8%) were performed via single-port access, while 464 (53.2%) were performed through two- or three-port approaches. Intraoperative sufentanil dose, surgical side, fluid infusion, transfusion requirements, duration of surgery, time to extubation, and the proportion of patients with drain tube removal beyond 3 days were comparable between groups.

Primary outcome

In the modified intention-to-treat analysis, the incidence of chronic pain at 3 months was significantly lower in the esketamine group than the control group (14.7% *vs* 21.2%; adjusted OR, 0.62; 95% CI, 0.43–0.90; P=0.013) (Table 3). Findings were consistent in the per-protocol analysis (14.3% *vs* 21.4%; adjusted OR, 0.60; 95% CI, 0.41–0.87; P=0.008). In sensitivity analysis using multiple imputation, the incidence of chronic pain at 3 months remained significantly lower in the

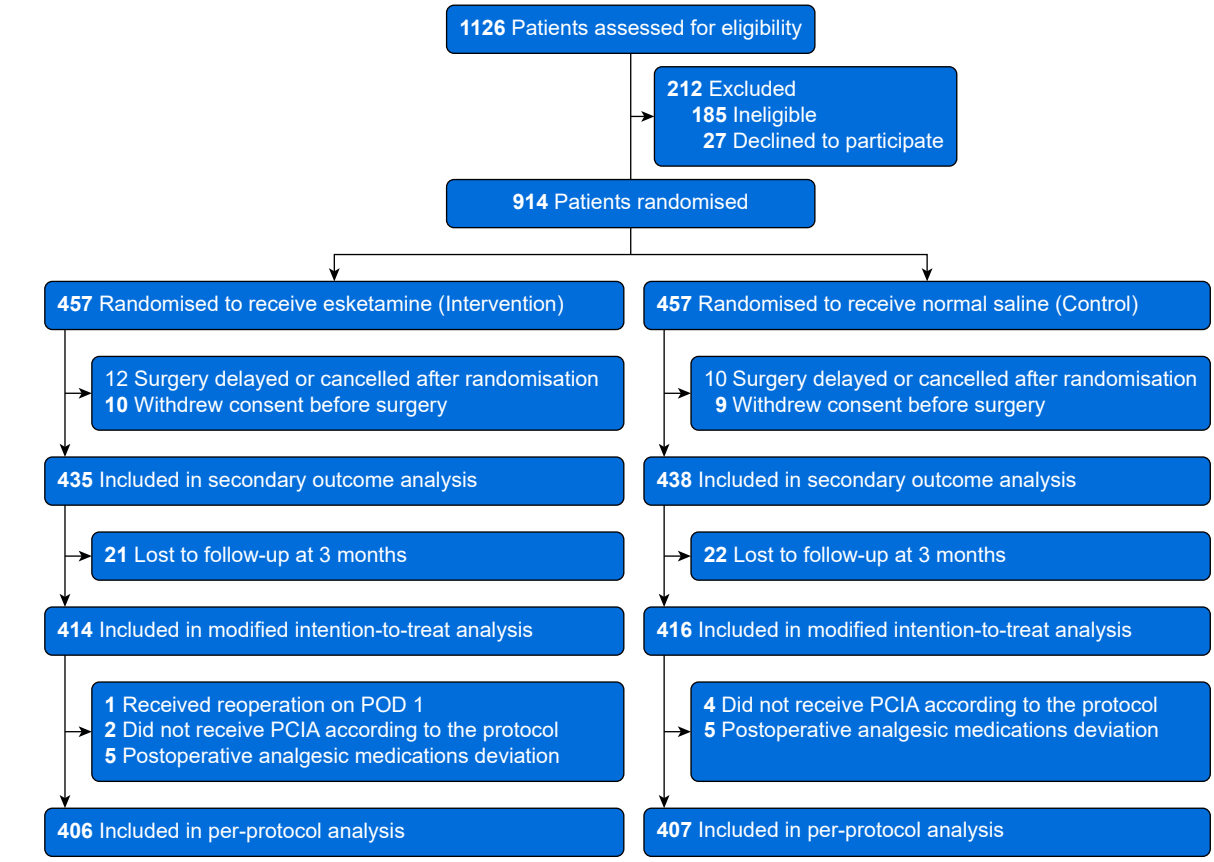


Fig 1. CONSORT flow diagram of patient enrolment, randomisation, and follow-up. CONSORT, Consolidated Standards of Reporting Trials; PCIA, patient-controlled i.v. analgesia; POD 1, postoperative day 1.

esketamine group than in the control group (adjusted OR, 0.65; 95% CI, 0.46–0.90; P=0.010).

The treatment effect on 3 month chronic pain was consistent across all prespecified subgroups, including study site (leading *vs* participating), sex (female *vs* male), BMI (<25 *vs* ≥25), diabetes mellitus (no *vs* yes), surgical type (wedge resection *vs* segmentectomy *vs* lobectomy), and number of surgical ports (single *vs* multiple) (Supplementary File 2, eFig. 1).

Secondary outcomes

No significant group-by-time interactions were observed for VAS pain scores at rest (P=0.820) or during coughing (P=0.084) over the 48 h period (Fig. 2). The estimated marginal mean difference between groups, averaged across the repeated time points over the 48 h period, was statistically significant both at rest (difference, −0.20; 95% CI, −0.32 to −0.07; P=0.002) and during coughing (difference, −0.41; 95% CI, −0.56 to −0.27; P<0.001). The sensitivity analysis yielded consistent results (Supplementary File 2, eFig. 2). No between-group difference was observed in the proportion of patients with NRS pain scores ≥1 during coughing at 7 days; however, this proportion was significantly lower in the esketamine group at 1 month. The need for supplemental analgesics was reduced in the esketamine group both within 48 h (13.8% *vs* 19.0%; adjusted OR, 0.65; 95% CI, 0.45–0.96; P=0.030) and 3 months (22.5% *vs* 30.1%; adjusted OR, 0.64; 95% CI, 0.47–0.89; P=0.007) (Table 3; Supplementary File 2, eTable 4). At 3 months, supplementary analgesics were required by seven patients in the esketamine group (two received oral tramadol, five received oral acetaminophen) and 15 patients in the control group (five received oral tramadol, 10 received oral acetaminophen).

Time to recovery of bowel function did not differ significantly between groups (adjusted HR, 0.91; 95% Cl, 0.79–1.05; P=0.199). Rates of in-hospital adverse events, including hypoxaemia, hypotension, nausea and vomiting, and itching were comparable between groups. The overall incidence of esketamine-related side-effects was also similar between groups (8.7% *vs* 6.9%; adjusted OR, 1.32; 95% CI, 0.80–2.19; P=0.276). None of the individual adverse events, including dreaminess, nightmares, hallucination, delirium, restlessness, orientation difficulty, laryngospasm, blurred vision, tachycardia, or salivation reached the statistical significance.

Exploratory outcomes

MMEs in PCIA were lower in the esketamine group (adjusted difference, −2.51 mg; 95% CI, −4.87 to −0.15 mg; P=0.037), and total MMEs within 48 h were also lower in the esketamine group (adjusted difference, −4.36 mg; 95% CI, −7.20 to −1.51 mg; P=0.003) (Table 4). Other in-hospital adverse events were comparable between groups. Intraoperative awareness

Table 1 Baseline characteristics. Data are reported as mean (standard deviation), median (interquartile range), or *n* (%). COPD, chronic obstructive pulmonary disease.

	Esketamine (*n*=435)	Control (*n*=438)	Standardised differences
Age (yr)	55.0 (48.0–60.0)	55.0 (47.0–60.0)	0.037
Sex			0.072
Female	266 (61.1)	283 (64.6)	
Male	169 (38.9)	155 (35.4)	
BMI (kg m^{-2})	23.3 (2.6)	23.2 (2.6)	0.022
Education (yr)	9 (9–12)	9 (9–13)	0.042
ASA physical status			0.111
1	327 (75.2)	308 (70.3)	
2	103 (23.7)	125 (28.5)	
3	5 (1.1)	5 (1.1)	
Smoking	68 (15.6)	59 (13.5)	0.061
Alcohol intake	12 (2.8)	6 (1.4)	0.098
History of thoracic surgery	8 (1.8)	8 (1.8)	0.001
History of malignancy	13 (3.0)	11 (2.5)	0.029
Comorbidity			
Hypertension	80 (18.4)	100 (22.8)	0.110
Diabetes mellitus	32 (7.4)	32 (7.3)	0.002
Coronary artery disease	5 (1.1)	7 (1.6)	0.039
Cerebrovascular disease	3 (0.7)	3 (0.7)	0.001
COPD	11 (2.5)	8 (1.8)	0.048
Haemoglobin (g dl^{-1})	13.2 (1.5)	12.9 (1.6)	0.157
Blood glucose (mM)	5.1 (4.6–5.7)	5.1 (4.6–5.8)	0.047
Creatinine (μM)	58.8 (51.0–69.0)	58.0 (50.4–67.0)	0.115
Trial sites			0.004
Leading site	93 (21.3)	93 (21.2)	
Participating sites	342 (78.6)	345 (78.8)	

occurred in one patient in the esketamine group, while no cases of delayed recovery or stroke were observed in either group. Postoperative sleepiness was similar between groups (21.1% *vs* 18.3%), and the median postoperative hospital stay was 4 days. The incidence of neuropathic pain at 3 months did not differ significantly between the esketamine and control groups (5.8% *vs* 7.9%). Individual neuropathic symptoms are detailed in Supplementary File 2, eFig. 3. Stabbing and sharp pain were the most frequently reported pain characteristics at both 1 and 3 months. At 1 month, fewer patients in the esketamine group reported stabbing pain, sharp pain, and heaviness compared with the controls; at 3 months, only the incidence of stabbing pain remained lower in the esketamine group.

Post hoc analysis

In *post hoc* analyses, three patients in the esketamine group and 10 in the control group had NRS pain scores ≥3 at rest at 3 months (0.7% *vs* 2.4%; adjusted OR, 0.28; 95% CI, 0.07–1.02; *P*=0.054), whereas the proportion of patients with NRS pain scores ≥3 during coughing was significantly lower in the esketamine group (2.9% *vs* 6.3%; adjusted OR, 0.39; 95% CI, 0.19–0.84; *P*=0.015) (Table 4). The DN4 interview total scores were comparable between the esketamine and control groups (adjusted difference, −0.08; 95% CI, −0.18 to 0.02; *P*=0.100).

Discussion

This multicentre randomised clinical trial found that perioperative low-dose esketamine infusion significantly reduced the incidence of CPSP in patients undergoing VATS lung resection. The beneficial effect on the primary outcome of CPSP at 3 months was consistent across the modified intention-to-treat, per-protocol, and multiple imputation analyses. Moreover, fewer patients in the esketamine group had cough-evoked pain scores ≥3 at 3 months. Low-dose esketamine infusion was not associated with increased incidence of adverse events. To our knowledge, this is the first multicentre randomised clinical trial to demonstrate that perioperative low-dose esketamine infusion reduces CPSP after VATS lung resection.

The high prevalence of CPSP after thoracoscopic procedures has been largely attributed to inadequately controlled acute postoperative pain, subsequent central sensitisation, and intercostal nerve injury.[6,25,26] Optimising perioperative pain management is therefore considered critical to mitigating CPSP. Multimodal analgesia is recommended in thoracic surgery to optimise analgesia and reduce opioid consumption.[1,27] Previous studies have shown that NMDA receptor activation plays a critical role in the induction and maintenance of central sensitisation driven by high-threshold primary afferent inputs.[28,29] Furthermore, experimental evidence has demonstrated that conditional deletion of spinal NMDA receptors prevents calcium-dependent neuronal death and attenuates the transition from acute to persistent pain, underscoring the pivotal role of NMDA receptor activation in pain chronification.[30]

Esketamine, the active S-enantiomer of ketamine, exerts potent NMDA receptor antagonism and provides approximately twice the analgesic potency of racemic ketamine.[31–33] Emerging evidence suggests that incorporating esketamine into multimodal analgesia may enhance acute postoperative pain control and reduce the requirement for supplemental analgesics.[32,34,35] Nevertheless, its efficacy in preventing CPSP

Table 2 Perioperative data. Data are reported as median (interquartile range) or *n* (%).

	Esketamine group (*n*=435)	Control group (*n*=438)	Standardised differences
Heart rate (beats min^{-1})			
Baseline	75 (67–80)	75 (67–78)	0.040
Induction	73 (66–81)	73 (68–81)	0.031
Skin incision	66 (59–74)	66 (59–72)	0.034
End of surgery	68 (62–74)	68 (61–72)	0.152
Extubation	80 (72–84)	78 (71–82)	0.192
Mean blood pressure (mm Hg)			
Baseline	94 (90–102)	93 (91–102)	0.013
Induction	90 (83–103)	90 (83–102)	0.030
Skin incision	86 (79–95)	85 (81–95)	0.067
End of surgery	86 (80–94)	85 (82–92)	0.081
Extubation	97 (89–103)	94 (91–101)	0.118
Anaesthetics and analgesics			
TIVA	215 (49.4)	213 (48.6)	0.016
Sevoflurane	220 (50.6)	225 (51.4)	
Sufentanil (μg)	40 (30–45)	40 (30–45)	0.102
Perioperative use of esketamine (mg)			
Total	60.9 (53.6–69.6)	0	-
During the surgery	16.2 (12.8–20.9)	0	-
After the surgery	44.6 (39.6–49.0)	0	-
Surgical procedure			
Wedge resection	74 (17.0)	82 (18.7)	0.063
Segmentectomy	131 (30.1)	121 (27.6)	
Lobectomy	230 (52.9)	235 (53.7)	
Surgical side			
Left	175 (40.2)	202 (46.1)	0.119
Right	260 (59.8)	236 (53.9)	
Number of ports			
Single	206 (47.4)	203 (46.3)	0.020
Multiple	229 (52.6)	235 (53.7)	
Intraoperative fluid infusion (ml)	900 (800–955)	900 (800–1000)	0.008
Transfusion	5 (1.1)	9 (2.1)	0.072
Duration of surgery (min)	100 (65–130)	95 (65–134)	0.019
Time to extubation (min)	18 (14–22)	16 (14–20)	0.059
Removal of drain tube >3 days	35 (8.0)	30 (6.9)	0.042

remains uncertain. Nielsen and colleagues[24] demonstrated that intraoperative esketamine (0.5 mg kg^{-1} bolus followed by a 0.25 mg kg^{-1} h^{-1} infusion until the end of surgery) decreased postoperative analgesic consumption and chronic pain 1 yr after spine surgery, while also improving labour market attachment in opioid-dependent patients. Conversely, Zhou and colleagues[12] reported that a single preoperative dose of esketamine (0.5 mg kg^{-1}) did not significantly affect the incidence of CPSP. This apparent lack of efficacy was most likely attributable to the short intervention window, which did not cover the critical period of surgical tissue injury and nociceptive activation. Notably, the duration of perioperative esketamine administration reported in the literature generally ranges from the intraoperative period to 48 h.[32,36,37] On this basis, we designed our regimen to deliver continuous i.v. esketamine infusion extending into the first 48 h after surgery, thereby ensuring adequate coverage of the entire acute phase of tissue injury.

Low-dose ketamine infusion (0.1–0.5 mg kg^{-1} h^{-1}) has been recommended to enhance postoperative analgesia; however, even at these doses, ketamine may induce adverse effects, particularly psychiatric adverse events.[38–41] Esketamine is less likely to elicit such side-effects.[33] In patients undergoing major abdominal surgery, low-dose esketamine (0.25 mg/kg bolus followed by 0.125 mg kg^{-1} h^{-1} for 48 h) was associated with increased psychiatric symptoms, whereas a mini-dose esketamine infusion (0.015 mg kg^{-1} h^{-1} without bolus) was not.[37] On the basis of this evidence, we used a stepwise esketamine regimen consisting of a low-dose bolus (0.1 mg kg^{-1}) followed by an intraoperative infusion (0.1 mg kg^{-1} h^{-1}) and a subsequent mini-dose infusion (0.015 mg kg^{-1} h^{-1}) for 48 h after surgery. This low-dose strategy did not increase psychiatric symptoms, consistent with a recent study by Zhang and colleagues.[42]

In this trial, sufentanil administration was titrated by the attending anaesthesiologist according to haemodynamic indicators (heart rate and blood pressure) rather than objective nociception monitoring. The median intraoperative esketamine dose was only 16 mg. Under these conditions, esketamine did not exhibit a clinically significant intraoperative opioid-sparing effect. However, we observed lower postoperative MME consumption in the esketamine group during the first 48 h. Thus, despite the lack of an intraoperative effect, perioperative esketamine infusion demonstrated an overall opioid-sparing effect.

With the introduction of the International Classification of Diseases and Related Health Problems 11th Revision (ICD-11), CPSP is now recognised as a multidimensional construct encompassing pain intensity, pain-related interference, and pain-related distress, thereby reflecting the biopsychosocial nature of chronic pain.[43] In our study, CPSP

Table 3 Study outcomes. Data are reported as median (interquartile range) or *n* (%). CI, confidence interval; HR, hazard ratio; NA, not applicable; NRS, numeric rating scale; OR, odds ratio. *Data are presented as median bowel function recovery time and corresponding HRs.

	Esketamine (*n*=435)	Control (*n*=438)	OR or HR (95% CI)	*P*-value	Adjusted OR or HR (95% CI)	Adjusted *P*-value
Primary outcome						
3 month NRS pain score on coughing ≥1						
Modified intention-to-treat analysis	61 (14.7) (*n*=414)	88 (21.2) (*n*=416)	0.64 (0.45–0.92)	0.016	0.62 (0.43–0.90)	0.013
Per-protocol analysis	58 (14.3) (*n*=406)	87 (21.4) (*n*=407)	0.61 (0.44–0.93)	0.008	0.60 (0.41–0.87)	0.008
Multiple imputation	-	-	0.63 (0.44–0.88)	0.007	0.65 (0.46–0.90)	0.010
Secondary outcomes						
7 day NRS pain score on coughing ≥1	285 (67.1) (*n*=425)	295 (69.3) (*n*=426)	0.90 (0.68–1.21)	0.493	0.90 (0.68–1.20)	0.485
1 month NRS pain score on coughing ≥1	136 (32.3) (*n*=421)	165 (39.2) (*n*=421)	0.74 (0.56–0.98)	0.037	0.73 (0.55–0.97)	0.032
Need for supplemental analgesics within 48 h	60 (13.8)	83 (19.0)	0.68 (0.47–0.98)	0.040	0.65 (0.45–0.96)	0.030
Need for supplemental analgesics within 3 months	98 (22.5)	132 (30.1)	0.67 (0.50–0.92)	0.011	0.64 (0.47–0.89)	0.007
Time to recovery of bowel function (h)*	14.0 (7.0–24.0)	13.5 (7.0–24.0)	0.92 (0.80–1.06)	0.257	0.91 (0.79–1.05)	0.199
Hypoxaemia	21 (4.8)	19 (4.3)	1.12 (0.59–2.06)	0.729	1.12 (0.59–2.11)	0.729
Hypotension	63 (14.5)	80 (18.3)	0.76 (0.53–1.08)	0.131	0.76 (0.53–1.09)	0.132
Nausea and vomiting	99 (22.8)	113 (25.8)	0.85 (0.62–1.16)	0.295	0.85 (0.62–1.16)	0.295
Itching	3 (0.7)	7 (1.6)	0.43 (0.12–1.53)	0.341	0.43 (0.11–1.66)	0.220
Esketamine-related side-effects	38 (8.7)	30 (6.9)	1.30 (0.81–2.16)	0.298	1.32 (0.80–2.19)	0.276
Dreaminess	15 (3.5)	13 (3.0)	1.17 (0.55–2.38)	0.706	1.17 (0.55–2.48)	0.687
Nightmares	1 (0.2)	1 (0.2)	1.00 (0.05–19.17)	>0.999	1.00 (0.06–16.22)	>0.999
Hallucination	3 (0.7)	2 (0.5)	1.51 (0.31–8.56)	0.686	1.51 (0.25–9.10)	0.651
Delirium	4 (0.9)	2 (0.5)	2.02 (0.47–10.68)	0.450	2.02 (0.37–11.10)	0.450
Restlessness	15 (3.5)	17 (3.9)	0.88 (0.44–1.78)	0.857	0.88 (0.44–1.79)	0.734
Orientation difficulty	1 (0.2)	0	NA	0.498	NA	0.970
Laryngospasm	0	0	NA	>0.999	NA	>0.999
Blurred vision	3 (0.7)	2 (0.5)	1.51 (0.31–8.56)	0.686	1.52 (0.25–9.31)	0.652
Tachycardia	5 (1.2)	4 (0.9)	1.26 (0.38–4.14)	0.752	1.26 (0.34–4.62)	0.727
Salivation	1 (0.2)	0	NA	0.498	NA	>0.999

assessment relied primarily on pain intensity at 3 months in the surgical region, consistent with the ICD-11 coding tool, which specifies that pain should begin or increase after surgery and be located in the area of the surgical procedure or its related anatomical region.[43] However, our study did not systematically evaluate pain-related interference or distress.

Substantial methodological heterogeneity in CPSP definitions exists across studies.[44–46] Most investigations use self-defined pain intensity thresholds to define CPSP, with some using cutoffs corresponding to at least moderate pain (NRS ≥3 or ≥4), which are generally considered clinically relevant for treatment.[47–49] Evidence from the PAIN OUT registry demonstrates that CPSP incidence varies markedly according to the pain intensity threshold applied (37.5%, 9.7%, and 5.7% when defined using NRS thresholds of ≥1, ≥3, and ≥4, respectively).[47] Previous studies have shown that CPSP after thoracic surgery may particularly interfere with activity-related functions, including coughing, getting out of bed, carrying groceries, and lying on the operated side.[50] Accordingly, several studies have specifically assessed chronic pain during coughing.[12,51] In our study, only three patients in the esketamine group and 10 in the control group had NRS pain scores ≥3 at rest at 3 months, indicating a low frequency of clinically meaningful pain at rest. Although a trend towards a reduction was observed (0.7% *vs* 2.4%), the between-group difference was not statistically significant. The low event rate may have limited the statistical power to detect a between-group difference, suggesting that a larger sample size would be needed to confirm this finding. In contrast, esketamine significantly reduced the proportion of patients with NRS pain scores ≥3 during coughing. As cough-evoked pain may more directly affect activity-related functioning, its reduction may be of particular clinical relevance. In addition, esketamine reduced supplemental analgesic requirements and total opioid consumption within the first 48 h. Notably, two patients in the esketamine group and five patients in the control group required oral opioids at 3 months. Given the relatively low absolute CPSP rates in this cohort, the analgesic benefits of esketamine may be more pronounced in higher-risk populations (e.g. patients undergoing major open surgery, opioid-tolerant individuals, or those requiring conversion to thoracotomy); however, direct extrapolation to these groups requires prospective validation.

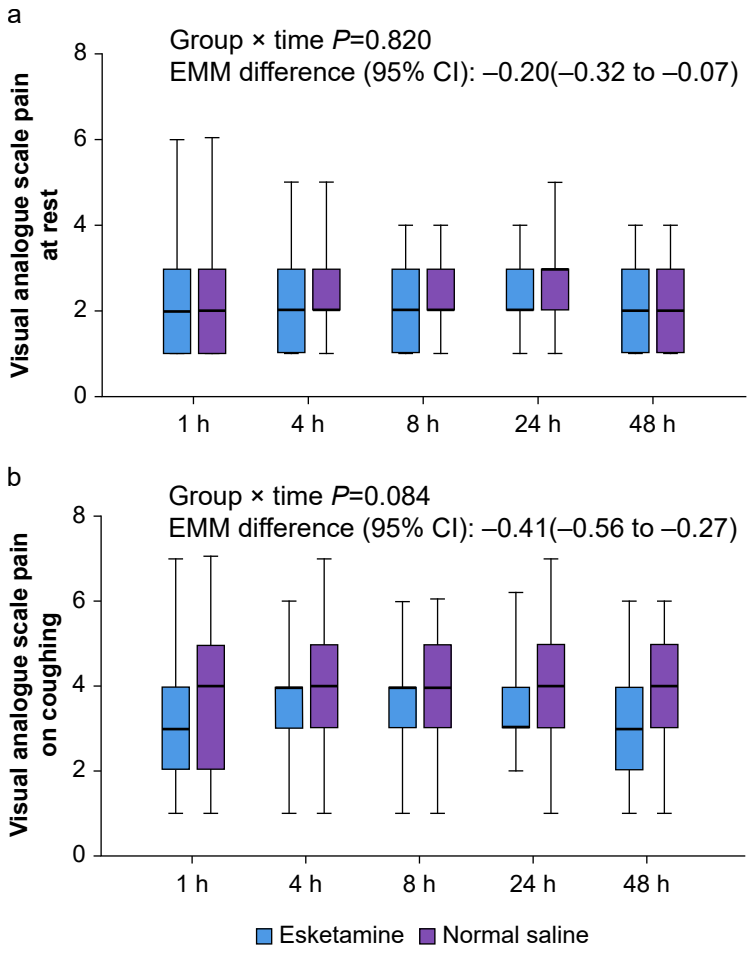


Fig 2. Visual analogue scale pain scores within 48 h after surgery. (a) Visual analogue scale pain at rest. (b) Visual analogue scale pain during coughing. Boxes represent interquartile ranges, horizontal black lines represent medians, and vertical lines represent 95% CIs. CI, confidence interval; EMM, estimated marginal mean.

The estimated marginal mean differences, reflecting the overall between-group differences during the first 48 h after surgery, were statistically significant both at rest (difference, −0.20) and during coughing (difference, −0.41). Nevertheless, the absolute between-group differences in acute pain were small. As these estimates represent average treatment effects, they may obscure potentially greater treatment effects at specific time points or in some individual patients. We speculate that the reduction in CPSP may have been mediated, at least in part, by attenuation of acute postoperative pain during the first 48 h, thereby limiting the transition from acute to chronic pain. In addition, the reduction in CPSP may also have been related to attenuation of NMDA receptor–mediated central sensitisation by esketamine infusion.[29] Although CPSP typically involves a neuropathic component,[52] only 5.8% of patients in the esketamine group and 7.9% of those in the control group met the symptom-based DN4 criteria for neuropathic pain, with mean DN4-interview total scores of 0.22 and 0.32, respectively. The esketamine group showed numerically lower rates of neuropathic pain and lower DN4-interview scores, although the between-group differences did not reach statistical significance. Further studies are warranted to clarify the potential effects of esketamine on neuropathic pain.

Limitations

This study has several limitations. First, the study population was confined to patients undergoing VATS, without including other minimally invasive thoracic procedures such as robot-assisted thoracic surgery. This restriction was justified by the predominance of VATS as the standard approach in the participating hospitals. Second, only a fixed stepwise esketamine regimen was evaluated in the present study, and the optimal dosing strategy remains to be determined. Third, our multimodal analgesic regimen excluded several common adjuncts (e.g. acetaminophen, tramadol, magnesium, and dexmedetomidine) to minimise confounding, which may limit generalisability to contemporary practice. Fourth, we used local infiltration with ropivacaine as part of multimodal analgesia, as it was routinely used for VATS lung resection at our centre.[53] However, PROSPECT (Procedure-Specific Postoperative Pain Management) guidelines recommend regional techniques (e.g.

Table 4 Exploratory outcomes and *post hoc* analysis. Data are reported as median (interquartile range), mean (standard deviation), or *n* (%). CI, confidence interval; DN4, Douleur Neuropathique 4; MME, morphine milligram equivalents; NA, not applicable; NRS, numeric rating scale; OR, odds ratio; PCIA, patient-controlled i.v. analgesia. *Data were analysed using a mixed-effects logistic regression or linear model, adjusting for baseline covariates (age, sex, type of surgery, and number of ports) as fixed effects, with trial site included as a random effect. †As the median and interquartile range were 0 in both groups, data are presented as mean (standard deviation).

	Esketamine (*n*=435)	Control (*n*=438)	OR or difference (95 CI %)	P-value	Adjusted OR or difference (95% CI)	Adjusted P-value
Exploratory outcomes						
MMEs in PCIA (mg)	90 (80.6–100.8)	93.1 (83.9–103.8)	−2.80 (−4.72 to −0.44)	0.008	−2.51 (−4.87 to −0.15)	0.037
MMEs within 48 h (mg)	90.7 (80.6–103.7)	95.2 (84.0–109.6)	−3.52 (−6.16 to −1.28)	0.002	−4.36 (−7.20 to −1.51)	0.003
Intraoperative awareness	1 (0.2)	0	NA	0.498	NA	0.886
Delayed recovery	0	0	NA	>0.999	NA	>0.999
Stroke	0	0	NA	>0.999	NA	>0.999
Pulmonary infection	3 (0.7)	3 (0.7)	1.01 (0.19–5.47)	0.993	1.01 (0.20–5.02)	0.993
Incision infection	2 (0.5)	1 (0.2)	2.02 (0.19–43.53)	0.567	2.02 (0.18–22.34)	0.567
Sleepiness	92 (21.1)	80 (18.3)	1.20 (0.86–1.68)	0.284	1.21 (0.86–1.70)	0.271
Length of postoperative hospital stay (days)	4 (3–5)	4 (3–5)	0 (0–0)	0.969	−0.01 (−0.20 to 0.19)	0.946
Neuropathic pain at 3 months	24 (5.8) (*n*=414)	33 (7.9) (*n*=416)	0.71 (0.42–1.22)	0.224	0.64 (0.35–1.19)	0.159
Pain characteristics at 1 month						
Burning	3 (0.7) (*n*=421)	2 (0.5) (*n*=421)	1.50 (0.25–11.46)	0.656	1.50 (0.25–9.05)	0.656
Stabbing	44 (10.5) (*n*=421)	70 (16.6) (*n*=421)	0.59 (0.39–0.87)	0.009	0.49 (0.31–0.78)	0.003
Sharp pain	36 (8.6) (*n*=421)	52 (12.4) (*n*=421)	0.66 (0.42–1.04)	0.073	0.54 (0.31–0.92)	0.025
Itching	29 (6.9) (*n*=421)	44 (10.5) (*n*=421)	0.63 (0.39–1.03)	0.068	0.63 (0.38–1.03)	0.063
Heaviness	7 (1.7) (*n*=421)	26 (6.2) (*n*=421)	0.26 (0.10–0.57)	0.002	0.26 (0.11–0.59)	0.001
Pain characteristics at 3 months						
Burning	2 (0.5) (*n*=414)	1 (0.2) (*n*=416)	2.02 (0.19–43.4)	0.568	2.01 (0.18–22.30)	0.568
Stabbing	25 (6.0) (*n*=414)	39 (9.4) (*n*=416)	0.62 (0.37–1.04)	0.074	0.55 (0.31–0.98)	0.043
Sharp pain	25 (6.0) (*n*=414)	32 (7.7) (*n*=416)	0.77 (0.45–1.32)	0.347	0.71 (0.38–1.31)	0.273
Itching	13 (3.1) (*n*=414)	17 (4.1) (*n*=416)	0.76 (0.36–1.58)	0.466	0.76 (0.36–1.59)	0.466
Heaviness	2 (0.5) (*n*=414)	8 (1.9) (*n*=416)	0.25 (0.04–1.00)	0.079	0.25 (0.05–1.17)	0.079
Post hoc* analysis						
3 month NRS pain score at rest ≥3	3 (0.7) (*n*=414)	10 (2.4) (*n*=416)	-	-	0.28 (0.07–1.02)	0.054
3 month NRS pain score on coughing ≥3	12 (2.9) (*n*=414)	26 (6.3) (*n*=416)	-	-	0.39 (0.19–0.84)	0.015
DN4 interview total score	0.22 (0.74) (*n*=414)†	0.32 (0.86) (*n*=416)†	-	-	−0.08 (−0.18 to 0.02)	0.100

paravertebral blocks, erector spinae plane blocks, or serratus anterior plane blocks) in VATS.[54] Therefore, the external validity of our findings warrants further investigation in settings where those multimodal analgesic approaches are standard. Fifth, we did not use an NRS pain score ≥3 as the threshold for CPSP, which is often considered clinically meaningful. Instead, we used a lower threshold (NRS ≥1) to enhance inclusiveness by capturing any persistent postoperative pain. Nevertheless, in a *post hoc* analysis, the esketamine group had a lower incidence of NRS pain scores ≥3 during coughing, suggesting a reduction in clinically meaningful pain. Finally, follow-up for chronic pain was restricted to 3 months, without extension to 6 months or 1 yr, thereby precluding assessment of longer-term outcomes.

Conclusions

In conclusion, perioperative low-dose esketamine infusion significantly reduced the incidence of chronic pain at 3 months after VATS lung resection. A reduction was also observed in clinically meaningful chronic pain during coughing. These findings support incorporating perioperative low-dose esketamine infusion into multimodal analgesic strategies for VATS.

Authors' contributions

Study design: QYW, XSS, YSL, FHJ
Data acquisition: QYW, JYZ, JQG, BL, YTG, FG, YQ, QL, HFL, JG
Manuscript drafting: QYW, JYZ, JQG, BL, YTG, FG, YQ, QL, HFL, JG
Data analysis: QYW, JYZ, JQG, BL, YTG, FG, YQ, QL, HFL, JG, HL, KP, XSS, YSL, FHJ
Data interpretation: QYW, JYZ, JQG, BL, YTG, FG, YQ, QL, HFL, JG, HL, KP, XSS, YSL, FHJ
Manuscript revision: KP, HL, XSS, YSL, FHJ
All authors have read and approved the final manuscript.

Acknowledgements

The authors greatly acknowledge the statistical assistance provided by Dr Yue-ping Shen and Dr Yao-yu Ying from the Department of Epidemiology and Biostatistics, School of Public Health, Medical College of Soochow University.

Funding

Institutional and departmental sources at the First Affiliated Hospital of Soochow University; National Natural Science

Foundation of China (82302456, 82471281); Jiangsu Province Medical Research General Project (H2023019), Jiangsu Province Key R&D Program (Social Development) (BE2023709); Suzhou Major Disease Multicentre Clinical Research Project (DZXYJ202401). The funders were not involved in the design or execution of the study or in the analysis and interpretation of the data.

Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2026.08.039.

References

1. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery after Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg* 2019; **55**: 91–115
2. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. *J Thorac Cardiovasc Surg* 2009; **138**: 419–25
3. Ye B, Wang M. Video-assisted thoracoscopic surgery versus thoracotomy for non-small cell lung cancer: a meta-analysis. *Comb Chem High Throughput Screen* 2019; **22**: 187–93
4. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. *Anesthesiology* 2006; **104**: 594–600
5. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. *Anesthesiology* 2018; **129**: 590–607
6. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; **393**: 1537–46
7. Chen Y, Chen J, Wang Q, et al. Safety and tolerability of esketamine in propofol based sedation for endoscopic variceal ligation with or without injection sclerotherapy: randomized controlled trial. *Dig Endosc* 2023; **35**: 845–54
8. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sánchez E, Gutiérrez-Rojas L, Meana JJ. Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs* 2018; **32**: 411–20
10. Bhatia A, Buvanendran A. Anesthesia and postoperative pain control-multimodal anesthesia protocol. *J Spine Surg* 2019; **5**(Suppl. 2): S160–5
11. Yan H, Chen W, Chen Y, et al. Opioid-free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: the use of intravenous and epidural esketamine. *Anesth Analg* 2023; **137**: 399–408
12. Zhou R, Zhang Y, Tang S, et al. A single preoperative dose of S-ketamine has no beneficial effect on chronic postsurgical pain in patients undergoing video-assisted thoracoscopic surgical lung lesion resection: a prospective randomized controlled study. *J Cardiothorac Vasc Anesth* 2023; **37**: 1433–41
13. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ* 2025; **389**, e081123
14. Lei Y, Liu H, Xia F, et al. Effects of esketamine on acute and chronic pain after thoracoscopy pulmonary surgery under general anesthesia: a multicenter-prospective, randomized, double-blind, and controlled trial. *Front Med (Lausanne)* 2021; **8**, 693594
15. Park JH, Lim BG, Kim H, Lee IO, Kong MH, Kim NS. Comparison of surgical pleth index-guided analgesia with conventional analgesia practices in children: a randomized controlled trial. *Anesthesiology* 2015; **122**: 1280–7
16. Ahn JH, Ahn HJ. Effect of thoracic epidural analgesia on recovery of bowel function after major upper abdominal surgery. *J Clin Anesth* 2016; **34**: 247–52
17. Spallone V, Morganti R, D'Amato C, Greco C, Cacciotti L, Marfia GA. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med* 2012; **29**: 578–85
18. Mu DL, Ding PP, Zhou SZ, et al. Cross-cultural adaptation and validation of the 3D-CAM Chinese version in surgical ICU patients. *BMC Psychiatry* 2020; **20**: 133
19. Chen WC, Bai YY, Zhang LH, et al. Prevalence and predictors of chronic postsurgical pain after video-assisted thoracoscopic surgery: a systematic review and meta-analysis. *Pain Ther* 2023; **12**: 117–39
20. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A prospective study of chronic pain after thoracic surgery. *Anesthesiology* 2017; **126**: 938–51
21. Widder A, Reese L, Lock JF, et al. Chronic postsurgical pain (CPSP): an underestimated problem after incisional hernia treatment. *Hernia* 2024; **28**: 1697–707
22. Jin D, Zhang Y, Zheng H, et al. The epidemiology of chronic postsurgical pain after video-assisted thoracic surgery (VATS-CPSP) in China: a multicentre prospective study. *J Thorac Dis* 2025; **17**: 2802–12
23. Semyonov M, Fedorina E, Shalman A, et al. Serratus anterior block for long-term post-thoracoscopy pain management. *J Pain Res* 2021; **14**: 3849–54
24. Nielsen RV, Fomsgaard JS, Nikolajsen L, Dahl JB, Mathiesen O. Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: a randomized clinical trial of opioid-dependent patients. *Eur J Pain* 2019; **23**: 455–60
25. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013; **154**: 95–102
26. Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain-from mechanisms to treatment. *Pain Rep* 2017; **2**, e588
27. Chen YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. *Anaesthesia* 2021; **76**(Suppl. 1): 8–17
28. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**: 293–9
29. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003; **97**: 1108–16
30. Inquimbert P, Moll M, Latremoliere A, et al. NMDA receptor activation underlies the loss of spinal dorsal horn neurons and the transition to persistent pain after peripheral nerve injury. *Cell Rep* 2018; **23**: 2678–89

31. White PF, Schüttler J, Shafer A, Stanski DR, Horai Y, Trevor AJ. Comparative pharmacology of the ketamine isomers. Studies in volunteers. *Br J Anaesth* 1985; **57**: 197–203
32. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth* 2021; **68**, 110071
33. Mion G, Himmelseher S. Esketamine: less drowsiness, more analgesia. *Anesth Analg* 2024; **139**: 78–91
34. Cheng X, Wang H, Diao M, Jiao H. Effect of S-ketamine on postoperative quality of recovery in patients undergoing video-assisted thoracic surgery. *J Cardiothorac Vasc Anesth* 2022; **36**: 3049–56
35. Mendola C, Cammarota G, Netto R, et al. S(+)-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. *Minerva Anestesiol* 2012; **78**: 757–66
36. Lahtinen P, Kokki H, Hakala T, Hynynen M. S(+)-ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. *Anesth Analg* 2004; **99**: 1295–301
37. Bornemann-Cimenti H, Wejbora M, Michaeli K, Edler A, Sandner-Kiesling A. The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial. *Minerva Anestesiol* 2016; **82**: 1069–76
38. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018; **43**: 456–66
39. Zhou L, Yang H, Hai Y, Cheng Y. Perioperative low-dose ketamine for postoperative pain management in spine surgery: a systematic review and meta-analysis of randomized controlled trials. *Pain Res Manag* 2022; **2022**, 1507097
40. Pouldar TM, Maher DP, Betz AW, et al. Adverse effects associated with patient-controlled analgesia with ketamine combined with opioids and ketamine infusion with PCA bolus in postoperative spine patients: a retrospective review. *J Pain Res* 2022; **15**: 3127–35
41. Gil LV, Mazzeffi MA, Cai Y, McLeod WW, Porter SB. Reasons for discontinuation of acute postoperative pain ketamine infusions: a retrospective case-control study. *Pain Pract* 2021; **21**: 759–65
42. Zhang Y, Cui F, Ma JH, Wang DX. Mini-dose esketamine-dexmedetomidine combination to supplement analgesia for patients after scoliosis correction surgery: a double-blind randomised trial. *Br J Anaesth* 2023; **131**: 385–96
43. Stamer UM, Lavand'homme P, Hofer DM, Barke A, Korwisi B. Definition of chronic postsurgical pain in the ICD-11: a narrative review of implications for anaesthesiology and pain medicine. *Br J Anaesth* 2026; **136**: 1319–29
44. Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001; **87**: 88–98
45. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008; **101**: 77–86
46. Werner MU, Kongsgaard UEI. Defining persistent postsurgical pain: is an update required? *Br J Anaesth* 2014; **113**: 1–4
47. Hofer DM, Lehmann T, Zaslansky R, et al. Rethinking the definition of chronic postsurgical pain: composites of patient-reported pain-related outcomes vs pain intensities alone. *Pain* 2022; **163**: 2457–65
48. Huang A, Azam A, Segal S, et al. Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service. *Pain Manag* 2016; **6**: 435–43
49. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study. *Pain* 2012; **153**: 1390–6
50. Bayman EO, Lennertz R, Brennan TJ. Pain-related limitations in daily activities following thoracic surgery in a United States population. *Pain Physician* 2017; **20**: E367–78
51. Kong L, Gao L, Zhang H, Wang X, Zhang J. Does preoperative hookwire localization influence postoperative acute and chronic pain after video-assisted thoracoscopic surgery: a prospective cohort study. *J Pain Res* 2023; **16**: 21–32
52. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618–25
53. Feng CD, Xu Y, Chen S, et al. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomised controlled trial. *Br J Anaesth* 2024; **132**: 267–76
54. Feray S, Lubach J, Joshi GP, Bonnet F, Van De Velde M, PROSPECT Working Group *of the European Society of Regional Anaesthesia and Pain Therapy. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia* 2022; **77**: 311–25

Handling Editor: Nadine Attal