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ORIGINAL RESEARCH

Esketamine as an Epidural Adjuvant for Postoperative Analgesia in Gynecological Malignancy Surgery: A Randomized Trial

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Objective: This study aims to evaluate the efficacy of esketamine as an epidural adjuvant in mitigating postoperative pain, particularly following the discontinuation of epidural analgesia in patients undergoing open surgery for gynecological malignancies.

Design: A randomized controlled trial.

Methods: Eighty-eight patients were randomized to receive either esketamine (0.4 mg/kg) combined with sufentanil and ropivacaine (eskatamine group) or sufentanil and ropivacaine alone (control group) via patient-controlled epidural analgesia. Primary outcomes included pain scores on postoperative day 3, assessed using the numeric rating scale. Secondary outcomes included pain scores on postoperative days 1 to 4, Quality of Recovery-15 scores, rescue analgesic requirements, and adverse events.

Results: The eskatamine group demonstrated a significant reduction in nocturnal pain intensity on postoperative day 2 compared with controls (median 3.0 vs 4.0, $P = 0.044$), with fewer patients requiring rescue analgesics on postoperative day 3 (13.4% vs 32.6%, $P = 0.036$). However, no significant differences were observed in rest pain, movement pain, or breakthrough pain across postoperative day 1–4. Subgroup analysis revealed higher Recovery-15 scores for moderate pain in the esketamine group (median 10 vs 9, $P = 0.048$). Transient dizziness was more frequent in the esketamine group (47.7% vs 23.3%, $P = 0.017$), but no persistent adverse effects were observed.

Conclusion: Esketamine, as an adjuvant in patient-controlled epidural analgesia, reduced nocturnal pain on postoperative day 2, shorten the moderate pain duration and lower rescue analgesics within 24 hours after the removal of analgesia device. However, it did not affect pain scores although less rescue analgesia was needed on postoperative day 3.

Keywords: esketamine, postoperative pain, epidural analgesia, recovery quality, gynecological malignancy

Introduction

Gynecologic malignancies may involve multiple pelvic and abdominal organs, necessitating extensive surgical resection.[1] Open surgery provides superior exposure of the operative field, facilitating comprehensive tumor removal and lymph node dissection to achieve curative intent. Moreover, laparoscopic approaches may carry a risk of tumor cell dissemination.[2] In open gynecologic oncology surgeries, pain mechanisms can be categorized into visceral and somatic pain. Visceral pain arises from direct tumor invasion, tumor-associated obstruction or perforation, tumor-induced inflammation or infection, and nerve traction or stimulation (activating splanchnic nerves). Somatic pain results from surgical trauma, inflammatory responses, and iatrogenic nerve injury. Collectively, these mechanisms contribute to postoperative pain. Epidural analgesia is widely regarded as a gold standard for postoperative pain management in major abdominal surgeries, including open gynecological malignancies, due to its superior blockade of nociceptive transmission.[3] However, its clinical utility is

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hampered by several persistent limitations. The application of epidural analgesia is limited in duration, and after the removal of the analgesic pump, some patients may still experience severe pain.[4] To address these challenges, adjuvant additives have been explored to synergize with local anesthetics.[5,6] Among these, N-methyl-D-aspartate (NMDA) receptor antagonists (e.g ketamine, esketamine) hold particular promise. Esketamine, the S(+)-enantiomer of ketamine, exhibits twice the analgesic potency of racemic ketamine and demonstrates prolonged pharmacokinetics (half-life: 15.4 hours), theoretically extending analgesia beyond epidural catheter removal.[7]

Recent advances in opioid-sparing strategies have underscored the potential of esketamine as a promising adjuvant agent. The study by Yan et al[8] demonstrated that substituting epidural opioids with esketamine in thoracoscopic surgery reduced the incidence of chronic postoperative pain. However, the exclusive use of epidural esketamine, compared to opioids alone, has been associated with an increased incidence of short-term postoperative pain. Therefore, we aim to investigate whether the combination of opioids and esketamine can mitigate acute postoperative pain. Furthermore, although intravenous esketamine has demonstrated efficacy in reducing postoperative moderate-to-severe pain,[9] its systemic administration may limit targeting of spinal NMDA receptors and increase neuropsychiatric side effects.[10] Xu et al found that intravenous administration of esketamine can lead to neuropsychiatric adverse reactions, such as hallucinations, vivid dreams, and dizziness.[11] In contrast, a direct comparison in lower extremity surgery revealed that epidural esketamine (0.2 mg/mL) reduced VAS scores compared with IV administration, without increasing sedation or psychiatric adverse effects.[12] Additionally, epidural esketamine permits direct delivery to spinal dorsal horn NMDA receptors, potentially enhancing analgesia while minimizing systemic exposure.[13] This hypothesis is supported by pharmacokinetic data demonstrating prolonged esketamine retention in cerebrospinal fluid following epidural administration (half-life: 15.4 hours vs 2.5 hours intravenously) [57]. As far as we know, there have been no clinical trials investigating the use of ketamine as an adjuvant in combination with opioids and local anesthetics for epidural analgesia.

To address the gap, we designed this prospective randomized controlled clinical trial, intending to verify our hypothesis that epidural esketamine could alleviate the rebound pain after removing the analgesic device.

Materials and Methods

Study Design

This is a prospective, randomized, double-blind, parallel-controlled clinical trial conducted at the Fudan University Shanghai Cancer Center in accordance with the CONSORT statement. The study protocol was approved by the Ethics Committee of the Fudan University Cancer Shanghai Center (Approval number: 2407300-10) and registered in the China Clinical Trials Registry (Registry number: ChiCTR2400091875). Written informed consent was obtained from each participant.

Inclusion Criteria

We recruited female participants aged 18–70 years who were scheduled for elective open surgery for gynecological malignancies. The inclusion criteria were as follows: American Society of Anesthesiologists (ASA) physical status I–III and body mass index (BMI) < 35 kg/m².

Exclusion Criteria

The exclusion criteria were as follows: (1) Inability to read or provide written informed consent. (2) Poorly controlled hypertension (ie, systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg). (3) Coagulation dysfunction. (4) Contraindications to epidural puncture. (5) Intraocular hypertension or glaucoma. (6) Known or suspected glaucoma. (7) Severe coronary heart disease, history of myocardial infarction within the past 6 months, or chest pain following recent mild activity.

Randomization and Blinding

Enrolled patients were randomly allocated to either the eskeamine group or the control group in a 1:1 ratio. Randomization was performed by an independent researcher using SPSS software. The results of the group allocation

were securely sealed in opaque envelopes. An anesthesiologist, not involved the anesthetic management, opened the envelope 1 hour before surgery. The independent anesthesiologist then prepared the analgesic medication and PCEA pump according to the allocated group. The anesthesiologists in charge of perioperative management remained blinded to the group allocation. After surgery, follow-up visits were conducted by a researcher who was also blinded to the group allocation.

Interventions

All of patients were monitored using electrocardiography, non-invasive blood pressure, and pulse oximetry when entering the operating room. Invasive arterial blood pressure and anesthesia depth with bispectral index (BIS) were monitored during the surgical procedures.

After central venous access was established, epidural puncture was performed at the T11-12 interspace, and a 5-cm catheter was inserted into epidural space. A test dose of 1% lidocaine (3 mL) was administered. Subsequently, the block level was assessed after the patient lies supine for 3 minutes. General anesthesia was induced intravenously with 2–3 mg/kg propofol, 0.3 μg/kg sufentanil, and 0.6–0.8 mg/kg rocuronium. And 5 mg dexamethasone and 3 mg granisetron were used before and after surgery, respectively, for postoperative nausea and vomiting (PONV) prevention.

Anesthesia depth was adjusted using target-controlled infusion of propofol, sevoflurane (0.5MAC) inhalation in an oxygen/air mixture, and 0.25% ropivacaine for epidural analgesia to maintain a BIS value between 40 and 60. The epidural administration protocol was as follows: An initial dose of 7–8 mL was administered in divided boluses before skin incision, with intervals of 3–5 minutes. Subsequently, 3–5 mL was administered every 1 hour. At the end of the procedure, 50 mg flurbiprofen was administered for multimodal analgesia. After surgery, sugammadex was administered at a dose of 4 mg/kg to antagonize muscle relaxation.

In postanesthesia care unit (PACU), all patients received a PCEA pump for pain control. For the esketamine group, the analgesic pump contained esketamine 0.4 mg/kg, sufentanil 100 μg, and ropivacaine 300 mg. For the control group, the analgesic regimen consisted of sufentanil 100 μg and ropivacaine 300 mg. The total capacity of the patient-controlled analgesia pump was 200 mL (sufentanil 0.5 μg/mL, ropivacaine 1.5 mg/mL), with a background infusion rate of 4.0 mL/h, a bolus dose of 4.0 mL, and a lockout interval of 15 minutes. Analgesia was maintained via the PCEA pump for 48 hours postoperatively. If a patient pressed the PCEA button during the lockout interval, the request was recorded as an additional press, but no additional analgesics were administered, which was defined as a failed press. Postoperative pain was evaluated using the Numeric Rating Scale (NRS) (NRS; 0 = no pain, 10 = worst imaginable pain).

A PACU nurse, who was not involved in anesthesia or postoperative follow-up, assessed the patient's NRS, checked for the presence of dizziness, delirium, nausea and vomiting, and recorded the patient's awakening time and medications administered in the PACU. Patients were discharged from the PACU once their Steward scores were greater than 6.

Outcomes

The primary outcome was the pain score on postoperative day 3 (POD3), assessed using the NRS. This included pain at rest, pain during activity, nocturnal pain, and the most severe pain experienced after removal of the analgesia pump.

Secondary outcomes included pain scores on postoperative days 1 (POD1), 2 (POD2), and 4 (POD4), as well as the Quality of Recovery-15 (QoR-15) score at POD3; the duration of surgery; pain scores and medication use in the PACU; the number of presses and failed presses on the PCEA pump; sleep duration and quality on POD3 and POD4; and complications related to ketamine (dizziness, nausea, vomiting, delirium, sleepiness, dreaming, nightmares). On POD1-4, an anesthesiologist, who was not involved in the management of anesthesia and was unaware of the group assignments, assessed the patient's postoperative pain. All follow-up evaluations were uniformly scheduled between 10:00 and 11:00 a.m. On postoperative day 2 (POD2), at approximately 11:00 a.m., the epidural analgesia pump was removed by a designated anesthesiologist, who was also responsible for conducting subsequent follow-up assessments. Additionally, the Quality of Recovery-15 (QoR-15) score was assessed on the POD3.

Sample Size Calculation

The sample size was calculated using PASS software (version 2021). Based on previous clinical trials, the mean score of breakthrough pain within 24 hours after removal of the analgesic pump was approximately 5 points. Since pump removal occurred at approximately POD2 11:00 a.m., this 24h period corresponds to POD3 assessments. Our primary outcome was the pain score on Postoperative Day 3 (POD 3). This specifically captured the peak intensity of breakthrough pain occurring between pump discontinuation on POD 2 and POD 3. We assumed that epidural esketamine would reduce the pain score to 4 points, with a standard deviation of 1.5. With a power of 80% and an α level of 0.05, 37 patients per group were required to detect differences. To account for a potential 20% dropout rate, 44 patients per group were finally enrolled in the trial.

Statistical Analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Continuous data were presented as mean ± standard deviation or median (interquartile range), as appropriate. Continuous outcomes were compared between groups using the Mann–Whitney *U*-test or independent samples *t*-tests, depending on their distribution. The non-normal distribution data and nocturnal pain scores were analyzed using the Wilcoxon signed-rank test. Categorical data were analyzed using the chi-square test. The significance level was set at 0.05 for all analyses. Statistical analyses were performed using SPSS software (Version 26.0, USA).

Results

A total of 88 patients undergoing open gynecological oncological surgery were assessed for eligibility. One patient, who was transferred to the ICU, was excluded from the analysis. All patients completed the follow-up. The study flowchart is presented in Figure 1.

The patient demographics were comparable between the two groups (Table 1), except that the prevalence of hypertension was higher in the esketamine group than in the control group (22.7% vs 7.0%; $P = 0.04$). Subgroup analysis by non-hypertension status (Table 2) revealed consistent reductions in POD2 nocturnal pain with esketamine in non-hypertensive patients ((1, 3) vs (1, 4.5); P=0.023).

No significant differences in pain intensity scores were found between the two groups at POD3 (Figure 2). However, significant differences in pain intensity at POD2 night were observed between the esketamine group and control group. The pain scores are presented in Table 3. In the esketamine group, less patients required rescue analgesics at POD3 (13.4% vs 32.6%; $P = 0.036$). Regarding adverse events, the incidence of postoperative dizziness was significantly higher in the esketamine group than in the control group (47.7% vs 23.3%; $P = 0.017$). However, no significant difference in dizziness was observed between the two groups on POD3. Additionally, no significant differences were observed in bolus analgesia times, incidences of PONV and nightmares. The median QoR-15 scores did not differ between the esketamine group and control group on POD3. Nevertheless, a subgroup analysis on QoR-15 indicated that moderate pain was less duration in the esketamine group than in the control group (median, 10 vs 9; $P = 0.048$). No significant differences were observed in postoperative severe pain, sleep quality, anxiety, and depression between the two groups.

No significant differences in other pain intensity scores during the postoperative first 4 days, including rest pain, movement pain, and breakthrough pain, which is shown in Figure 3.

Discussion

Our study demonstrated that the addition of esketamine to PCEA solution significantly reduced the incidence of nocturnal pain on POD2 and alleviated moderate pain duration on POD3 in patients undergoing open gynecological malignancy surgery. However, no significant differences were observed in rest pain, movement pain, or breakthrough pain during the POD1-4 days. Although hypertension prevalence differed at baseline, subgroup analysis analyses demonstrated that this imbalance did not confound our primary findings. These findings suggest that the analgesic effect of epidural esketamine is time-dependent and may be related to its pharmacokinetic profile and mechanism of action.

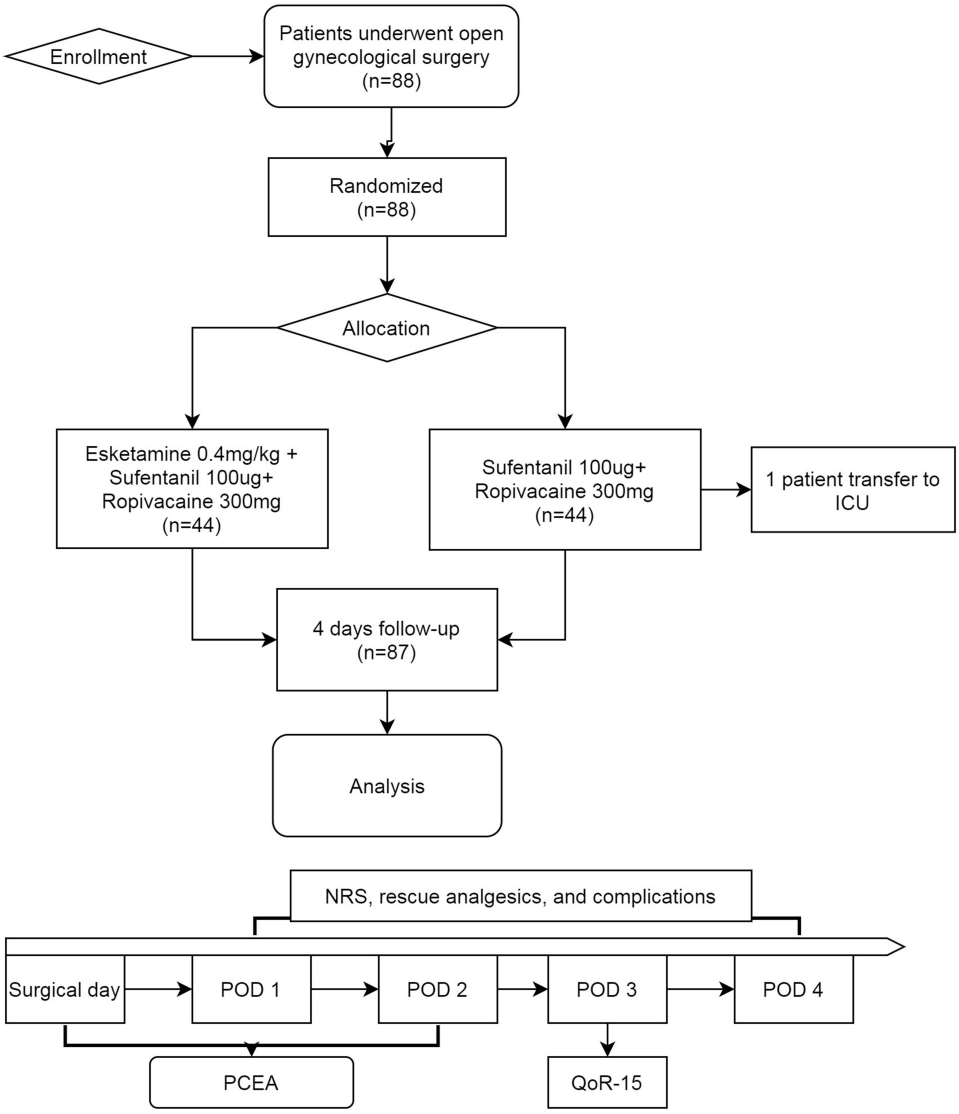

Figure 1 The flow chart of the study.
Abbreviations: ICU, Intensive Care Unit. POD, postoperative day; NRS, Numeric Rating Scale; QoR-15, Quality of Recovery-15.

The observed reduction in nocturnal pain at POD2 may be attributed to the dual action of esketamine as an NMDA receptor antagonist and a modulator of central sensitization. Surgical trauma induces peripheral nociceptor activation and spinal dorsal horn synapses glutamate release, which promotes NMDA receptor-mediated hyperalgesia and wind-up phenomena.[14] By blocking NMDA receptors, esketamine likely attenuates central sensitization, thereby mitigating delayed pain amplification following cessation of epidural analgesia.[15] This is consistent with previous studies showing that NMDA antagonists reduce rebound pain following withdrawal of regional anesthesia.[16,17] Actually, intravenous esketamine could reduce postoperative pain scores, decrease the incidence of rebound pain following cessation of thoracic paravertebral block, and reduces opioid consumption.[18] Epidural esketamine also can lower opioid consumption, provide better postoperative analgesia, reduce the rescue analgesics.[7] Moreover, the extended half-life of esketamine (15.4 hours) may prolong its analgesic effects,[7] potentially explaining the reduction in nocturnal pain at POD2 rather than at earlier timepoints. However, the transient nature of this effect underscores the necessity for optimized dosing regimens to sustain therapeutic benefits.

The modest improvement in moderate pain at POD3 by evaluating the QoR-15, coupled with the lack of differences in other pain metrics, raises concerns regarding the adequacy of the esketamine dose (0.4 mg/kg/48h) used in this trial. In

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Table 1 Demographic and Clinical Characteristics at Baseline

	Esketamine Group (n=44)	Control Group (n=43)	P Value
Age (year)	54.9 ± 10.0	51.7 ± 11.5	0.18
BMI	23.4 ± 3.0	23.2 ± 3.2	0.77
Diagnosis			0.72
Ovarian cancer	23 (52.3%)	26 (60.5%)	
Endometrial cancer	9 (20.4%)	8 (18.6%)	
Cervical cancer	12 (27.3%)	9 (20.9%)	
ASA score			0.85
I	11 (25%)	10 (23.3%)	
II	33 (75%)	33 (76.7%)	
Surgical duration (min)	120 (98, 180)	127 (100, 180)	0.61
Transfusion	2 (4.6%)	4 (9.3%)	0.38
Intraoperative bleeding	200 (125, 300)	200 (200, 300)	0.36
Hypertension	10 (22.7%)	3 (7.0%)	0.04
Diabetes	3 (6.8%)	5 (11.6%)	0.44
Intraoperative ropivacaine dosage (mg)	33.8 (26, 38.8)	35 (30, 45)	0.1
Chemotherapy history	13 (29.6%)	10 (23.3%)	0.51

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 Principal Findings in Non-Hypertensive Patients

	Esketamine Group N=34	Control Group N=40	*P*-Value
POD1 Pain intensity max	2 (1, 4)	2 (1, 3)	0.63
POD2 Pain intensity max	2.6 ± 1.4	2.3 ± 1.8	0.33
POD2 nocturnal pain	2 (1, 3)	2.5 (1, 4.5)	0.023
POD3 rest pain	1.0 ± 0.9	1.1 ± 1.1	0.53
POD3 pain on activity	2 (1, 3)	2 (1, 3)	0.92
POD3 Pain intensity max	2.8 ± 1.7	3.4 ± 1.9	0.16
Rescue analgesia on POD3	5 (14.7%)	13 (32.5%)	0.075
Moderate pain in QoR-15	10 (8, 10)	8.5 (8, 10)	0.028
Severe pain in QoR-15	10 (10, 10)	10 (9.5, 10)	0.30
QoR-15	113 ± 14	110 ± 12	0.26
Bolus in PCA	1 (0, 3)	1 (0, 2.5)	0.86

Abbreviations: POD, postoperative day; PCA, patient-controlled analgesia; QoR-15, Quality of Recovery-15.

the context of pain assessment utilizing the QoR-15 scale, a lower score is associated with prolonged pain duration and inferior recovery quality. Previous studies employing higher doses esketamine doses (1–2 mg/kg/48h) have reported more pronounced reductions in postoperative pain scores and opioid consumption.[19–21] Esketamine has been utilized both intravenously and epidurally. For instance, Zhang et al demonstrated that the addition of 1 mg/kg esketamine to PCIA reduced moderate-to-severe pain by 40% in patients undergoing thoracoscopic surgery.[9] A recent study reported that 25 mg esketamine was added to PCEA.[8] Our lower epidural esketamine dose may have resulted in subtherapeutic plasma concentrations, which were insufficient to fully suppress NMDA receptor activity beyond the immediate post-operative period. The dissociation between significant POD2 nocturnal pain reduction and non-significant POD3 pain scores may reflect harmacokinetic-pharmacodynamic Mismatch; Epidural esketamine's CSF half-life (15.4 hr) predicts subtherapeutic concentrations at POD3 assessment. Pharmacometric modeling indicates: POD2 night (36 hr): CSF (esketamine) ≈ 55 ng/mL (> IC_{50} 40 ng/mL),POD3 (48 hr): CSF (esketamine) ≈ 25 ng/mL (< IC_{50}).This aligns with

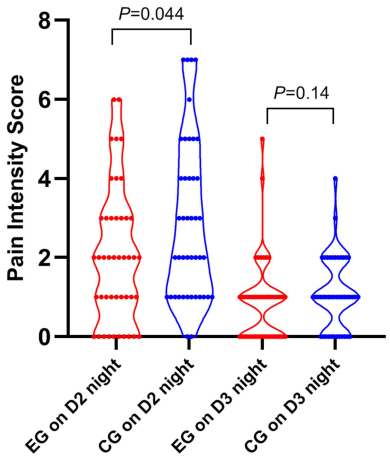

Figure 2 Violin plots of nocturnal pain intensity in two groups at postoperative 2 and 3 days.
Notes: The nocturnal pain at POD2 was lower in the esketamine group compared with that in the control group (P=0.044). Within the violin plot, the solid line represents the median, and the dotted line represents the quartile.
Abbreviations: EG, esketamine group; CG, control group.

animal data showing NMDA blockade efficacy requires >35 ng/mL CSF levels.[7] On the other hand, differential modulation of pain phenotypes; Early nocturnal pain on POD 2 primarily involves surgically induced incisional pain and visceral traction pain, while later pain predominantly arises from central sensitization. By POD3, pain transitions to neuroplasticity phases, in which cytokine pathways dominate.[22] Additionally, heterogeneous pain trajectories post-pump removal may account for these findings. It exhibits individualized differences in pain experience and therapeutic response. Future trials should explore dose escalation strategies while balancing potential side effects, such as dizziness, which was more prevalent in our esketamine group.

The selective reduction in nocturnal pain at POD2 has significant clinical implications. Postoperative sleep disruption, which is often exacerbated by nighttime pain, is associated with delayed recovery and increased morbidity.[23] By targeting this critical period, esketamine may enhance sleep quality and patient satisfaction,[24] despite the absence of differences in overall pain scores. This is consistent with our subgroup analysis, which showed improved QoR-15 scores for moderate pain in the esketamine group. However, the lack of significant differences in overall QoR-15 scores suggests that the benefits of the current regimen may be confined to specific pain dimensions rather than overall recovery metrics. NRS reduction in POD2 nocturnal pain translates to decrease in sleep-interrupting pain episodes (NRS>4). This aligns with ERAS benchmarks where NRS≤3 enables uninterrupted >4hr sleep blocks - faster functional recovery in patients.[25]

Table 3 Comparisons of Postoperative Outcomes Between the Two Groups

	Esketamine Group (n=44)	Control Group (n=43)	*P* Value
Bolus analgesia (times)	1 (0, 3)	1 (0, 3)	0.53
Rescue analgesia on D3	6 (13.4%)	14 (32.6%)	0.036
PONV	23 (52.3%)	19 (44.2%)	0.45
Dizzy	21 (47.7%)	10 (23.3%)	0.017
Dizzy on D3	9 (20.5%)	6 (14.0%)	0.42
Nightmare	3 (6.8%)	2 (4.7%)	0.66
QoR-15	113 ± 13	110 ± 12	0.26
QoR-15 mid pain	10 (8, 10)	9 (8,10)	0.048
QoR-15 severe pain	10 (10, 10)	10 (9, 10)	0.19
QoR-15 sleep quality	5.5±2.8	5.4±2.6	0.76
QoR-15 anxiety	8±1.1	8±1.3	0.85
QoR-15 depression	7.8±1.4	7.6±1.3	0.46

Abbreviations: PONV, Postoperative Nausea and Vomiting; QoR-15, the Quality of Recovery-15.

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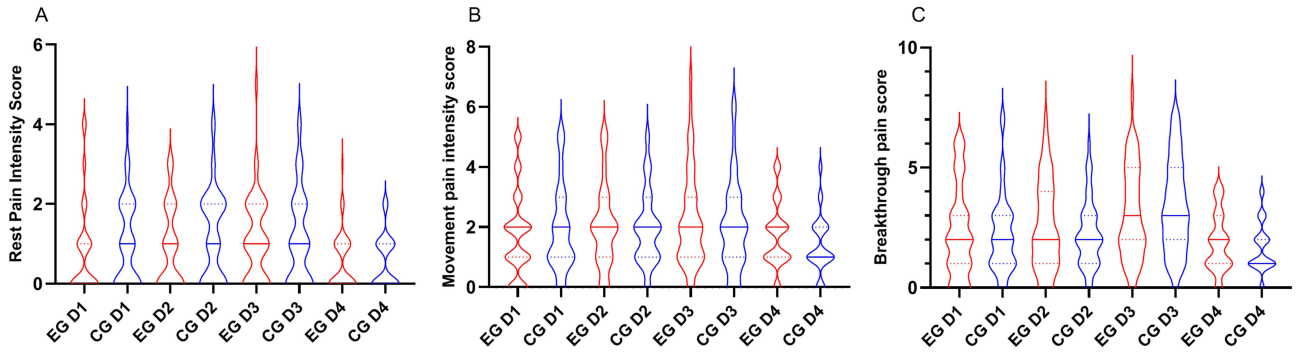

Figure 3 Violin plots of rest pain, movement pain and breakthrough pain intensity in two groups at multiple time points.
Notes: (**A**) Rest pain intensity. (**B**) Movement pain intensity. (**C**) Breakthrough pain intensity. Within the violin plot, the solid line represents the median, and the dotted line represents the quartile.
Abbreviations: EG, esketamine group, CG, control group.

Clinicians might consider time-limited esketamine infusions tailored to the peak rebound pain period (eg, 24–48 hours after pump removal) to maximize cost-effectiveness and minimize side effects.

Although epidural esketamine has shown promise, its role within multimodal analgesia framework warrants further discussion. Recent evidence supports the combination of NMDA antagonists with other adjuvants (e.g, gabapentinoids or COX-2 inhibitors) to synergistically target both peripheral and central pain pathways.[26,27] For instance, a randomized trial by Zhang et al demonstrated that the combination of intravenous esketamine with dexmedetomidine reduced improved analgesia and sleep quality after scoliosis correction surgery.[28] Another randomized trial by Yan et al found that combining epidural esketamine with intravenous parecoxib reduced both acute and chronic post-thoracotomy pain compared to either drug alone.[8] In our study, all patients received flurbiprofen as a part of standardized multimodal protocol, which may have mitigated differences in baseline pain scores between the two groups. Future studies should evaluate the additive effects of esketamine in opioid-sparing regimens or in populations with contraindications to NSAIDs.

We also observed that the incidence of dizziness was higher in the treatment group than in the control group. Nevertheless, our data showed no clinically significant differences in QoR-15 scores between the two groups. A Meta-analysis, including 18 RCTs, has demonstrated that the use of ketamine or esketamine in the perioperative period does not increase the risk of adverse events.[29] The higher incidence of dizziness in the esketamine group underscores the need for cautious dose titration. Notably, dizziness did not persist in POD3 or achieve clinically meaningful differences in QoR-15 scores, suggesting it is transient and manageable symptom. This is consistent with meta-analysis indicating that perioperative ketamine does not increase severe adverse events. However, clinicians should monitor neuropsychiatric symptoms, particularly in vulnerable populations (eg, the elderly or those with a psychiatric history.[30,31]

Our study has several limitations. First, the single-center design and moderate sample size limit its generalizability. Although our power calculation was robust for the primary endpoint, larger multicenter trial is needed to validate these findings across diverse surgical populations. Second, the fixed timing of analgesic pump removal may have introduced bias, as individual variability in pain trajectories could influence nocturnal pain severity. Adaptive protocols allowing pump removal based on pain thresholds rather than fixed durations might better capture the true efficacy of epidural esketamine. Third, we did not measure plasma inflammatory markers and esketamine levels, which could provide mechanistic insights into interindividual variability. Future research should incorporate pharmacokinetic-pharmacodynamic modeling to identify optimal dosing schedules and to guide biomarker-informed analgesia. While transient dizziness was more frequent with esketamine (47.7%), its resolution by POD3 and absence of neuropsychiatric events support epidural safety. This contrasts with IV esketamine studies reporting 20–30% hallucination rates, suggesting route-specific advantages.

Conclusion

In summary, the addition of esketamine to PCEA significantly reduced nocturnal pain on POD2 during which analgesia device has been removed, and improved moderate pain, as assessed by the QoR-15 in patients undergoing open gynecological surgery. Moreover, the use of epidural esketamine at a dosage of 0.4 mg/kg was found to be safe and feasible, without clinically significant adverse effects. Based on our safety findings and dose-response trends, it is necessary to investigate dose escalation of esketamine. While higher doses may prolong the duration of pain relief, they may also increase adverse effects. Further studies utilizing an up-and-down biased coin design are required to determine the optimal dosage and associated adverse events. Alternatively, investigating a multimodal strategy combining low-dose esketamine and gabapentinoids to simultaneously target spinal NMDA receptors and peripheral sensitization pathways may enhance efficacy for gynecological visceral pain.

Abbreviations

EG, esketamine group; CG, control group; ICU, Intensive Care Unit; POD, postoperative day; NRS, Numeric Rating Scale; QoR-15, Quality of Recovery-15; PONV, Postoperative Nausea and Vomiting; BMI, body mass index; ASA: American Society of Anesthesiologists.

Data Sharing Statement

Deidentified individual participant data will be made available. The shared data will include CRFs and Excel-formatted datasets. Data is available on request from the corresponding author. Study protocol, statistical analysis plan, and informed consent template will be accessible. The data will become publicly available immediately upon online publication of the article and will remain accessible for 10 years.

Ethics Approval and Informed Consent

Ethical approval was obtained from the ethics committees of the Fudan University Shanghai Cancer Center (No: 2407300-10). Written informed consent was obtained from all participants. The study complies with the Declaration of Helsinki.

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Huanyu Luo and Yuecheng Yang are co-first authors for this study. We thank all the participants who conducted and assisted in this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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