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CLINICAL TRIAL REPORT

Comparison of the Effective Dose 90 (ED90) and Clinical Outcomes of Fentanyl Versus Esketamine for Analgesia in Hysteroscopy: A Two-Part, Randomized, Double-Blind Trial

Jun Du, Chan Li, Mei Huang, Xiarong Qin

Department of Anesthesiology, Zhejiang Hospital, Hangzhou, Zhejiang, 310030, People's Republic of China

Correspondence: Xiarong Qin, Department of Anesthesiology, Zhejiang Hospital, Hangzhou, Zhejiang, 310030, People's Republic of China, Email zjyy_qxr@163.com

Background: Hysteroscopy is a minimally invasive procedure that can nonetheless elicit considerable pain, especially during cervical dilation. While fentanyl is widely used for analgesia, its application is limited by side effects such as respiratory depression. Esketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising alternative due to its potent analgesic effects and safer profile. This study aimed to determine and compare the effective dose 90 (ED90) of these drugs for preventing physical movements and to evaluate their efficacy and safety.

Methods: This two-part, prospective, randomized, double-blind trial enrolled patients scheduled for hysteroscopy. In Part 1, the ED90 of intravenous fentanyl (0.25–2.00 μg/kg) and esketamine (0.15–0.50 mg/kg) was determined using a sequential allocation biased-coin design (SABCD). The SABCD was implemented independently for each drug, with a targeted enrollment of 60 participants per group; ultimately, 56 participants per group were included in this dose-finding phase. In Part 2, clinical outcomes and adverse events were compared in an additional set of 56 patients per group, all of whom received the predetermined ED90 of their assigned drug.

Results: The ED90 of fentanyl was 1.424 μg/kg (95% confidence interval [CI]: 1.322–1.618 μg/kg), compared to 0.423 mg/kg (95% CI: 0.368–0.569 mg/kg) for esketamine. The two groups exhibited comparable efficacy in physical movements inhibition and total propofol consumption. However, the esketamine group demonstrated a markedly improved safety and recovery profile. Specifically, patients receiving esketamine reported significantly less propofol injection pain (fentanyl group vs esketamine group, 25% vs 7.1%; relative risk [RR], 0.4; 95% CI: 0.2–0.8; $P = 0.019$), experienced significantly faster emergence from anesthesia (7.0 [5.0, 9.5] vs 6.0 [5.0, 8.0]; median difference [MD], −1.0; 95% CI: −2.0–0; $P = 0.029$), and maintained better hemodynamic stability. Crucially, the incidence of respiratory depression was significantly lower in the esketamine group (26.8% vs 3.6%; RR, 0.2; 95% CI: 0.06–0.6; $P = 0.001$). Furthermore, the esketamine group showed a significantly greater reduction in Hospital Anxiety and Depression Scale (HADS) scores at the one-month follow-up than the fentanyl group (4.0 [3.0, 4.0] vs 2.0 [1.0, 2.0]; MD, −2.0; 95% CI: −2.0–−2.0; $P < 0.001$).

Conclusion: At equipotent ED90 doses, esketamine provides analgesia equivalent to fentanyl during hysteroscopy, while conferring additional advantages, such as reduced injection pain, faster emergence, superior cardiorespiratory stability, and potential psychological benefits.

Registration: Chinese Clinical Trial Registry ChiCTR2500106429.

Keywords: fentanyl, esketamine, ED90, hysteroscopy, analgesia

Introduction

Hysteroscopy is a minimally invasive endoscopic procedure widely used for the diagnosis and treatment of intrauterine pathologies.[1] While generally considered safe, the procedure can cause significant patient discomfort and pain in the absence of anesthesia, particularly during cervical dilation and uterine distention.[2] Consequently, effective analgesia is essential to ensure patient comfort, facilitate surgical conditions, and improve overall perioperative experience.

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Fentanyl, a potent synthetic μ-opioid receptor agonist, is commonly used for analgesia during brief surgical procedures like hysteroscopy due to its rapid onset and short duration of action.[3] However, its use is associated with well-known adverse effects, including respiratory depression, nausea and vomiting, chest wall muscle stiffness,[4] and the potential for hyperalgesia,[5] which can pose significant challenges in the day surgery setting. To mitigate these limitations, there is a growing need for alternative analgesic agents with improved safety profiles.

Esketamine, the S-enantiomer of ketamine, is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist.[6] It possesses potent analgesic and anesthetic properties and has gained increasing use in procedural sedation and analgesia. Compared to racemic ketamine, esketamine offers approximately twice the analgesic potency and a potentially more favorable side effect profile.[7] Its unique mechanism of action, which dissociates analgesic from sedative effects while preserving respiratory drive, makes it an attractive alternative to opioids like fentanyl. Furthermore, accumulating evidence suggests that esketamine holds considerable potential in treating depression and may exert a positive influence on perioperative anxiety.[8,9]

Determining the optimal analgesic dose for hysteroscopy aims to maximize efficacy while minimizing adverse effects, thereby optimizing patient safety and satisfaction in day surgery. This objective is especially pertinent because preoperative anxiety, which can be exacerbated by variable quality of online information,[10] may negatively impact procedural tolerance and outcomes. While prior studies have provided specific ED95 values for esketamine in hysteroscopy, with reported doses of 0.254 mg/kg and 0.489 mg/kg respectively,[11,12] the ED90 for this procedure remains less precisely characterized and has not been directly compared with the corresponding ED90 of fentanyl. Therefore, this study aims to prospectively determine and compare the ED90 of fentanyl and esketamine for preventing physical movements during hysteroscopy and to evaluate their clinical efficacy and safety profiles when administered at these equipotent doses. In addition, the impact of esketamine on postoperative anxiety and depression will also be assessed.

Methods

This prospective, randomized, double-blind study comprised two parts. Part 1 aimed to determine the ED90 of fentanyl and esketamine for preventing physical movements in patients undergoing hysteroscopy. Part 2 compared the clinical efficacy and adverse events of fentanyl and esketamine at their respective ED90 doses in these patients.

Ethics and Registration

The study was conducted at Zhejiang Hospital in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline. Approval was obtained from the Zhejiang Hospital Institutional Review Board (Approval No: 2024–118K), and the study was registered with the Chinese Clinical Trial Registry (Registration No: ChiCTR2500106429). Written informed consent was obtained from all participants prior to enrollment. The study adhered to the principles of the Declaration of Helsinki.

Study Subjects

The screening of consecutive patients scheduled for hysteroscopy was planned for the period between August and December 2025.

Inclusion Criteria

(1) Voluntary acceptance of hysteroscopy under intravenous anesthesia; (2) age 18–60 years, body mass index (BMI) 20–25 kg/m^2; (3) American Society of Anesthesiologists (ASA) physical status I–II.

Exclusion Criteria

(1) Severe respiratory or circulatory system diseases; (2) severe mental or neurological disorders; (3) substance abuse; (4) hepatorenal dysfunction; (5) visual or hearing impairment; (6) allergy to esketamine, fentanyl, or propofol; (7) contra-indications for esketamine.

Discontinuation Criteria

(1) Protocol violation (eg, intraoperative change to other anesthesia techniques, postoperative loss to follow-up); (2) suspension of research (eg, surgery duration > 1 hour, withdrawal of consent, severe adverse events).

Sample Size Estimation

Part 1 Based on a previous study,[13] and the requirement for estimating ED90 with moderate confidence using an up-and-down design, 120 patients were enrolled (60 per group).

Part 2 The primary outcome measure for this study was total propofol consumption. Based on existing literature,[14,15] the administration of low-dose esketamine (< 0.5 mg/kg) was associated with a 15.3% to 36.7% reduction in total propofol requirements compared to conventional opioids. Sample size estimation was performed using hysteroscopic anesthesia data from our institutional database between July and August 2024. Retrospective analysis of 353 patients receiving fentanyl demonstrated a mean propofol consumption of 332.8 ± 118.4 mL (mean ± SD). Using an α level of 0.05 and 80% power (1-β = 0.8),[16] with the assumption of equal variance between the fentanyl and esketamine groups, a sample size of 51 patients per group was required to detect a 20% reduction in propofol consumption. Accounting for an anticipated 10% dropout rate, 56 participants per group were enrolled in the randomized trial. It should be noted that the final sample size deviated from the initial registry record of 60 participants per group; this adjustment was made to ensure adequate statistical power while optimizing resource allocation.

Randomization and Masking

A statistician uninvolved in the study generated the random allocation sequence using an online tool. Sequences were sealed in opaque envelopes. After obtaining informed consent, an anesthesia nurse opened the envelope and prepared the study drug (fentanyl or esketamine) in a separate room. The calculated drug dose for each participant was diluted with normal saline to a final volume of 10 mL in identical syringes, using a pre-designed Word Processing System (WPS) spreadsheet. Resident doctors, blinded to the study groups, administered the medication and collected data. Patients and outcome assessors were also blinded.

Study Protocol

All patients underwent preoperative anesthesia assessment the day before surgery, provided informed consent, and were instructed to fast from solids for 8 hours and clear liquids for 2 hours. Upon arrival in the operating room, standard monitoring (vital signs: heart rate [HR], mean arterial pressure [MAP], systolic arterial pressure [SAP], diastolic arterial pressure [DAP], respiratory rate [RR], pulse oxygen saturation [SpO_2]) was established using a patient monitor. Oxygen was administered via mask at 5 L/min. Venous access was established for fluid (sodium lactate Ringer's solution at 5–10 mL/kg/h) and drug administration. Patient identity was verified by the attending nurse, chief surgeon, and an uninvolved anesthesiologist. Patients were positioned in lithotomy. After surgical site disinfection and sterile draping, the study analgesic (fentanyl [Batch: AB41003011, Yichang Humanwell Pharmaceutical, Hubei, China] or esketamine [Batch: 241123BP, Hengrui Pharmaceutical, Jiangsu, China]) was administered. A bolus of propofol (2 mg/kg, Diprivan®, Corden Pharma SPA, Caponago, Italy) was then given, followed by a continuous propofol infusion (4–12 mg/kg/h) to maintain a modified observer's assessment of alertness/sedation (MOAA/S) scale score ≤ 1.

Part 1 The dose of fentanyl or esketamine for each patient was determined using the SABCD. The maximum dosage limits were established based on clinical experience and supporting literature.[16] Dose ranges were divided into 8 levels. The possible doses for fentanyl were as follows: 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00 μg/kg. The possible doses for esketamine were as follows: 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50 mg/kg. The starting doses were 0.25 μg/kg fentanyl and 0.15 mg/kg esketamine. Occurrence of physical movements during cervical dilation was defined as analgesic failure, and the subsequent patient's dose was increased (fentanyl: + 0.25 μg/kg; esketamine: + 0.05 mg/kg). Absence of movements was defined as analgesic success; the next patient's dose had an 11% (1/9) probability of decreasing one level or an 89% (8/9) probability of remaining unchanged. The allocation sequence generated by the statistician using WPS Spreadsheets was provided to the anesthesia nurse in opaque envelopes.

Part 2 Patients received the ED90 doses of fentanyl or esketamine as determined in Part 1. Hysteroscopy was performed by experienced gynecologists, with cervical dilation achieved using sequential metal dilators. During the procedure, a collaborative assessment protocol was implemented: if the gynecologist reported observable patient movement, an attending anesthesiologist immediately evaluated the patient using the physical movements pain scale. A score ≥ 2 prompted an intravenous propofol bolus (20–50 mg), which was repeated as needed until the score was ≤ 1. Perioperative adverse events were managed promptly. Hypertension, defined as SBP > 180 mmHg, DBP > 100 mmHg, or a > 20% increase from baseline, was treated with intravenous urapidil (10 mg). Hypotension, defined as SBP < 90 mmHg, DBP < 60 mmHg, or a > 20% decrease from baseline, was treated with intravenous norepinephrine (8 μg). Tachycardia (HR > 100 bpm) was managed with esmolol (10 mg), while bradycardia (HR < 50 bpm) was treated with atropine (0.5 mg). Respiratory depression was defined as SpO_2 < 95% for >10 seconds, necessitating manual airway opening. Postoperatively, patients recovered in the post-anesthesia care unit (PACU), where the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale score was assessed every minute until reaching ≥ 4. Psychiatric symptoms (including dissociation, delirium, drowsiness, agitation, hallucinations, diplopia, and memory impairment) were assessed by the PACU nurse. Mild psychiatric symptoms, dizziness, and headache were managed with observation, while severe cases prompted consultation with a neurologist. Nausea and vomiting were treated with a combination of dexamethasone (5 mg) and tropisetron (5 mg). Vital signs were recorded at PACU discharge and at hospital discharge. At the one-month follow-up, the Hospital Anxiety and Depression Scale (HADS) was administered via an electronic questionnaire.

Outcomes

Part 1 Outcomes in this part comprised physical movements and serious adverse reactions.

Part 2 This study was conducted with eight predefined observation time points: 30 minutes before anesthesia induction (T_0); when the MOAA/S scale score reached ≤ 1 after propofol administration (T_1); during cervical dilation using the largest dilator (T_2); at surgical completion (T_3); when MOAA/S scale score recovered to ≥ 4 (T_4); upon PACU discharge (T_5); at hospital discharge (T_6); and 1 month post-discharge (T_7). The primary outcomes included total propofol consumption, propofol dosage, and propofol infusion rate. The secondary outcomes encompassed addition frequency of propofol, propofol injection pain, incidence of physical movements, arousal time, duration of stay in the PACU, satisfaction scores of patients and surgeons, NRS scores at T_4 and T_5, HADS scores at T_0 and T_7, and vital signs at T_0–T_6. Anesthesia related adverse events included dizziness, headache, hypertension, hypotension, tachycardia, bradycardia, respiratory depression, nausea and vomiting, and psychiatric symptoms.

Scales

Modified Observer's Assessment of Alertness/Sedation Scale

0: No response to painful trapezius squeeze;
1: Responds only after painful trapezius squeeze;
2: Responds only after mild prodding or shaking;
3: Responds only after repeated or loud name calls;
4: Lethargic response to normal tone name calls;
5: Quick response to normal tone name calls.
≤ 1 point: indicative of adequate surgical sedation; ≥ 4 points: recovery from sedation.[17]

Propofol Injection Pain Scale

0: Negative response to questioning;
1: Pain reported in response to questioning only, without any behavioural signs;
2: Pain reported in response to questioning and accompanied by a behavioural sign, or pain reported spontaneously without questioning;
3: Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears.[18]
0–1 point: propofol injection pain negative; 2–3 points: propofol injection pain positive.[19]

Physical Movements Pain Scale

0: No physical movements;
1: Painful facial expressions or slight physical movements not affecting surgery;
2: Moderate physical movements affecting surgery;
3: Intense physical movements halting surgery.
0–1 point: effective inhibition of physical movements.[20]

Numerical Rating Scale

The NRS scores ranged from 0 (no pain) to 10 (worst pain imaginable).
1–3 points: mild pain; 4–6 points: moderate pain; 7–10 points: severe pain.

Hospital Anxiety and Depression Scale

The HADS scale consists of two subscales, assessing anxiety and depression levels separately. Each item consists of four options (scored from 0 to 3 points), and the total scores for each subscale are calculated by summing the individual item responses.
0–7 points: a negative result; 8–10 points: mild levels of depression or anxiety; 11–14 points: moderate levels of depression or anxiety; 15–21 points: severe levels of depression or anxiety.[21]

Satisfaction

Patients and surgeons rated anesthesia effect satisfaction from 0 (very unsatisfied) to 10 (very satisfied).

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 and GraphPad Prism 8.0. Both the a priori sample size estimation and the post hoc power analysis were performed using G*Power 3.1.9.7. Probit regression determined the median effective dose (ED50), ED90, and 95% confidence intervals (CI) for fentanyl and esketamine. Continuous data are presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical data are expressed as frequencies (percentages). Normality was assessed using the Shapiro–Wilk test ($P > 0.05$ indicating normality). For vital signs, non-parametric methods were applied across all time points for methodological consistency. Normally distributed continuous variables were compared between groups using independent *t*-tests. Non-normally distributed continuous variables were compared using Mann–Whitney *U*-tests (between groups at single time points) or Wilcoxon signed-rank tests (within-group changes over time), with Bonferroni correction for multiple comparisons. Categorical variables were analyzed using Chi-square or Fisher's exact tests, as appropriate. Between-group differences for continuous outcomes are presented as median differences (MDs) with 95% CIs, estimated using the Hodges-Lehmann estimator. For categorical outcomes, effect sizes are presented as relative risks (RRs) with 95% CIs, estimated via the Koopman asymptotic score method. Flowcharts were created using WPS Presentation. Drug up-down sequences and dose-response curves were generated using WPS Spreadsheets. Perioperative trends in vital sign parameters were plotted using GraphPad Prism 8.0. A P value of < 0.05 was considered statistically significant.

Results

Patient Demographics and Baseline Characteristics

A total 291 patients undergoing hysteroscopy were screened. Recruitment was completed on September 10, 2025, after the planned sample size was met. Throughout the recruitment period, 59 individuals were excluded due to not meeting the eligibility criteria or declining participation. 120 participants were enrolled in an independent cohort for Part 1; 8 were subsequently excluded (surgery > 1 hour: n = 3; withdrawal: n = 5). A separate, distinct cohort of 112 patients were enrolled in Part 2. Enrollment followed a CONSORT diagram (Figure 1). Demographic and baseline characteristics were comparable between the fentanyl and esketamine groups in Part 2 ($P > 0.05$; Table 1).

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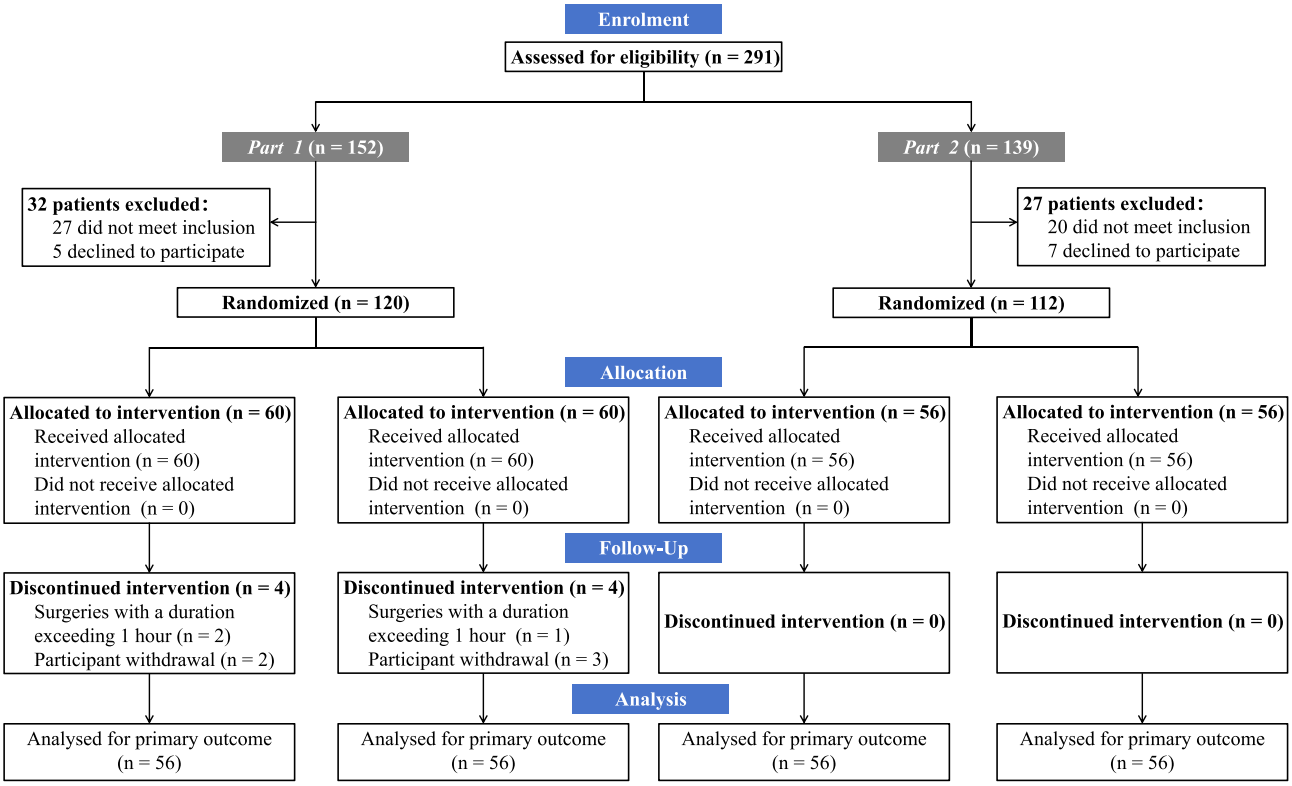

Figure 1 Patient enrollment flow diagram following Consolidated Standards of Reporting Trials guidelines.

ED50 and ED90 of Fentanyl and Esketamine

The up-down biased-coin dose allocation sequences for fentanyl and esketamine are shown in Figure 2A and B, respectively. Probit regression analysis yielded an ED50 of 1.232 μg/kg (95% CI: 0.886–1.332 μg/kg) and ED90 of 1.424 μg/kg (95% CI: 1.322–1.618 μg/kg) for fentanyl. For esketamine, the ED50 was 0.255 mg/kg (95% CI: 0.009–0.320 mg/kg) and ED90 was 0.423 mg/kg (95% CI: 0.368–0.569 mg/kg). The dose-response curves of fentanyl and esketamine are presented in Figure 3.

Primary and Secondary Outcomes

Analyses revealed no significant differences between the fentanyl and esketamine groups across multiple measures. These included the total propofol dose (fentanyl group vs esketamine group, 250.0 [200.0, 323.0] vs 257 [220.0, 356.5];

Table 1 Demographic and Baseline Characteristics of the Two Groups in Part 2

Characteristics	Fentanyl Group (n = 56)	Esketamine Group (n = 56)	*P* value
Age (years)	41 (31.5, 46.5)	36.5 (30, 43.5)	0.218
Height (m)	1.60 (1.57, 1.64)	1.60 (1.58, 1.63)	0.960
Weight (kg)	55 (51.3, 60.0)	56.8 (52.8, 62.3)	0.319
BMI (kg/m^2)	21.6 (20.1, 23.5)	22.2 (20.8, 24.3)	0.280
ASA, I (n%)	32 (57.14)	32 (57.14)	1.000
Operative time (min)	18.5 (14.5, 24.5)	19.0 (14.0, 27.5)	0.963
Fluid transfusion volume (mL)	300 (200, 450)	300 (250, 400)	0.934
Blood loss (mL)	10.0 (5.0, 10.0)	10.0 (5.0, 10.0)	0.990

Notes: Data are presented as median (interquartile range) or number of patients (%). A *P* value of < 0.05 was considered statistically significant.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

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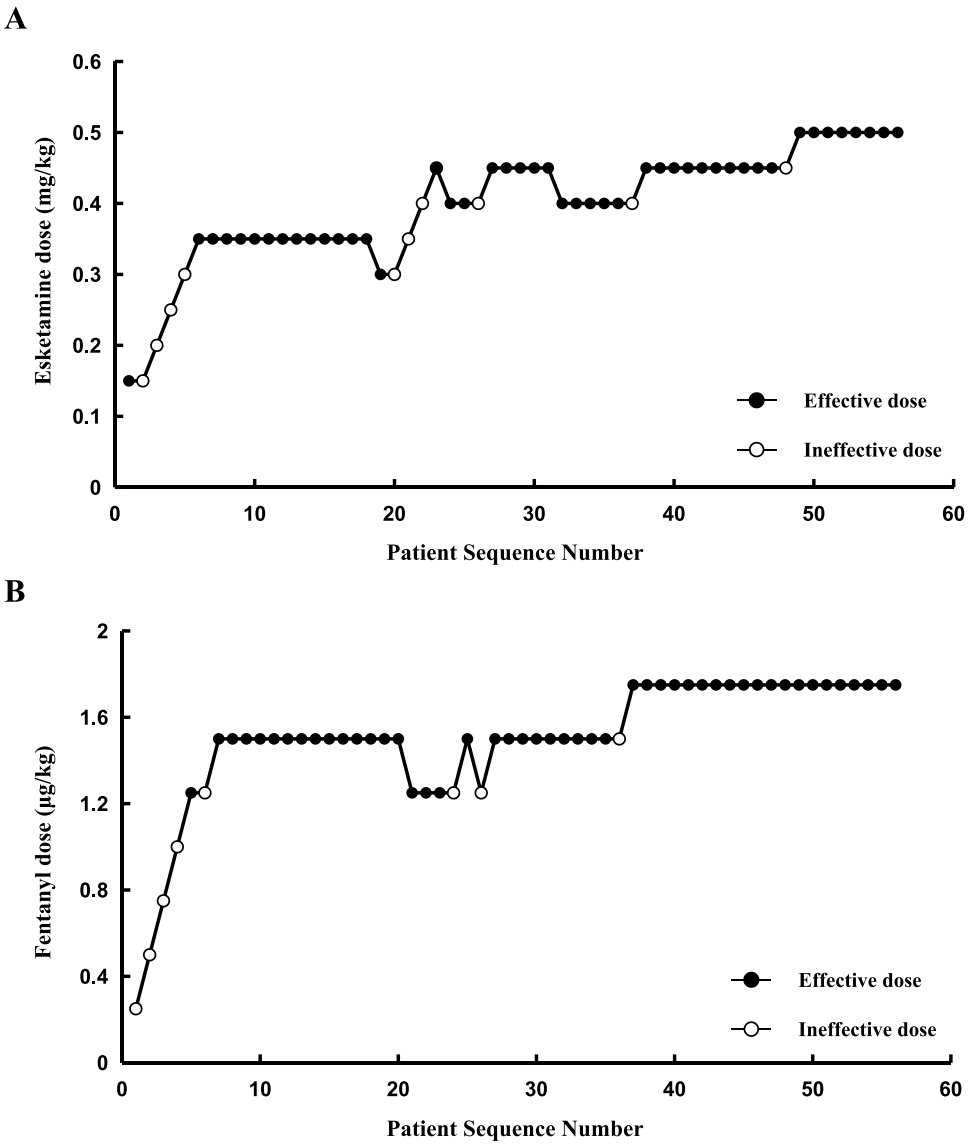

Figure 2 The up-down sequences of administered doses of esketamine (**A**) and fentanyl (**B**). Hollow circles represent physical movements (analgesic failure) and solid circles represent no physical movements (analgesic success).

median difference [MD], 10.0; 95% CI: −14.0–50.0; $P = 0.370$), propofol dosage (4.7 [3.8, 5.7] vs 5.0 [3.9, 5.8]; MD, 0.2; 95% CI: −0.3–0.8; $P = 0.442$), and propofol infusion rate (15.3 [11.7, 19.6] vs 15.7 [12.5, 19.2]; MD, 0.4; 95% CI: −1.7–2.3; $P = 0.679$), addition frequency of propofol (0 [0, 1] vs 0 [0, 1]; MD, 0; 95% CI: 0–0; $P = 0.586$), incidence of physical movements (5.4% vs 5.4%; relative risk [RR], 1.0; 95% CI: 0.4–1.7; $P = 1.000$), duration of stay in the PACU (30.0 [30.0, 35.0] vs 30.0 [30.0, 45.0]; MD, 0; 95% CI: 0–0; $P = 0.180$), satisfaction scores of the surgeons (10.0 [9.0, 10.0] vs 10.0 [9.0, 10.0]; MD, 0; 95% CI: 0–0; $P = 0.939$), satisfaction scores of the patient (10.0 [10.0, 10.0] vs 10.0 [10.0, 10.0]; MD, 0; 95% CI: 0–0; $P = 0.530$), NRS scores at T_4 (0 [0, 0] vs 0 [0, 0]; MD, 0; 95% CI: 0–0; $P = 0.731$), and NRS scores at T_5 (0 [0, 0] vs 0 [0, 0]; MD, 0; 95% CI: 0–0; $P = 0.146$). However, the esketamine group demonstrated a significantly reduced perception of pain during propofol injection (25% vs 7.1%; RR, 0.4; 95% CI: 0.2–0.8; $P = 0.019$) and a shorter arousal time (7.0 [5.0, 9.5] vs 6.0 [5.0, 8.0]; MD, −1.0; 95% CI: −2.0–0; $P = 0.029$) compared to the fentanyl group. Furthermore, exploratory analysis showed that HADS scores at 1 month post-discharge were significantly lower in the esketamine group (4.0 [3.0, 4.0] vs 2.0 [1.0, 2.0]; MD, −2.0; 95% CI: −2.0–−2.0; $P < 0.001$) (Table 2).

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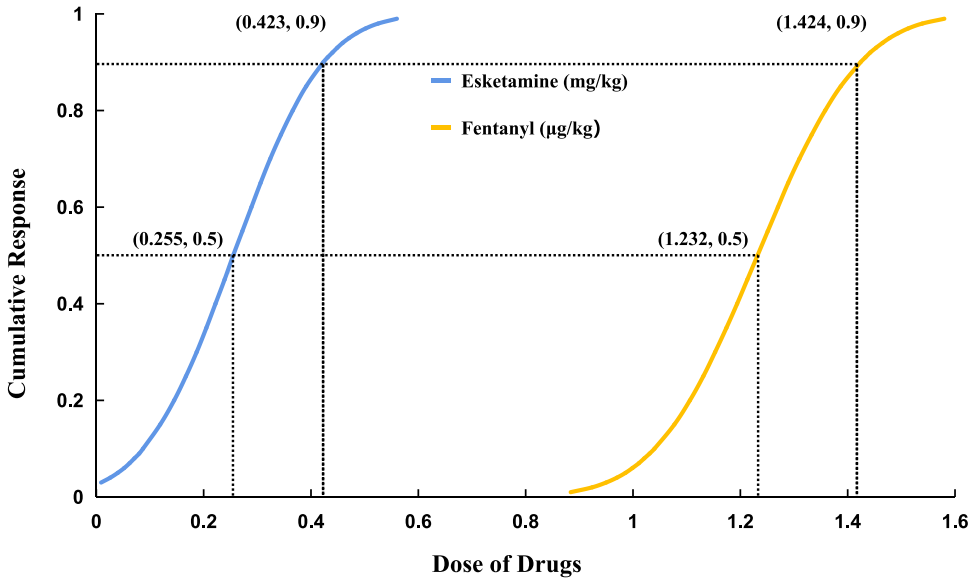

Figure 3 Dose-response curves for esketamine and fentanyl. The intersection of dashed and solid lines represents the esketamine (blue solid line) and fentanyl (Orange solid line) of ED50 and ED90.

Vital sign measurements for both groups at different time points are detailed in Table 3 and Figure 4. Notably, the esketamine group exhibited significantly higher HR at T_1, T_2, and T_6 ($P < 0.05$). Similarly, MAP was significantly elevated in the esketamine group at all recorded time points (T_1, T_2, T_3, T_4, and T_5) ($P < 0.05$). SAP values were significantly higher at T_1, T_2, T_3, and T_5, while DAP was significantly increased at all time points (T_1–T_5) ($P < 0.05$) in the esketamine group. RR were also significantly higher in the esketamine group at T_1, T_2, T_3, and T_4 ($P < 0.05$). In contrast, no significant differences in SpO_2 were observed between the groups at any time point. Overall, esketamine counteracted propofol-induced hemodynamic depression more effectively, resulting in higher blood pressure and heart rate values compared to the fentanyl group.

Table 2 Comparison of the Clinical Indicators Between the Two Groups

Indicators	Fentanyl Group (n = 56)	Esketamine Group (n = 56)	Estimated Effects (95% CI)	*P* Value
Total propofol consumption (mg)	250.0 (200.0, 323.0)	257 (220.0, 356.5)	MD, 10.0 (−14.0 to 50.0)	0.370
Propofol dosage (mg/kg)	4.7 (3.8, 5.7)	5.0 (3.9, 5.8)	MD, 0.2 (−0.3 to 0.8)	0.442
Propofol infusion rate (mg/kg/h)	15.3 (11.7, 19.6)	15.7 (12.5, 19.2)	MD, 0.4 (−1.7 to 2.3)	0.679
Administration frequency of propofol (times)	0 (0, 1)	0 (0, 1)	MD, 0 (0 to 0)	0.586
Propofol injection pain, yes (n%)	14 (25.0)	4 (7.1)	RR, 0.4 (0.2 to 0.8)	0.019
Physical movements, yes (n%)	3 (5.4)	3 (5.4)	RR, 1.0 (0.4 to 1.7)	1.000
Arousal time (minutes)	7.0 (5.0, 9.5)	6.0 (5.0, 8.0)	MD, −1.0 (−2.0 to 0)	0.029
Duration of stay in the PACU (minutes)	30.0 (30.0, 35.0)	30.0 (30.0, 45.0)	MD, 0 (0 to 0)	0.180
Surgeon satisfaction score (points)	10.0 (9.0, 10.0)	10.0 (9.0, 10.0)	MD, 0 (0 to 0)	0.939
Patient satisfaction score (points)	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	MD, 0 (0 to 0)	0.530
NRS score, T_4 (points)	0 (0, 0)	0 (0, 0)	MD, 0 (0 to 0)	0.731
NRS score, T_5 (points)	0 (0, 0)	0 (0, 0)	MD, 0 (0 to 0)	0.146
HADS score, T_0 (points)	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	MD, 0 (0 to 0)	0.716
HADS score, T_7 (points)	4.0 (3.0, 4.0)	2.0 (1.0, 2.0)	MD, −2.0 (−2.0 to −2.0)	< 0.001

Notes: Data are presented as median (interquartile range) or number of patients (%). T_0, time of 30 minutes before anesthesia induction; T_4, time of the MOAA/S scale score ≥ 4; T_5, time of leaving the PACU; T_7, time of one month after discharge. A *P* value of < 0.05 was considered statistically significant.
Abbreviations: PACU, post anesthesia care unit; NRS, numerical rating scale; HADS, Hospital Anxiety and Depression Scale; CI, confidence interval; MD, median difference; RR, relative risk.

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Table 3 Comparison of the Perioperative Vital Sign Parameters Between the Two Groups

Vital Sign Parameters	Time	Fentanyl Group (n = 56)	Esketamine Group (n = 56)	Estimated Effects (95% CI)	*P* value
HR, median	T_0	71 (62, 76) (47, 98)	70 (65, 78) (58, 102)	MD, 3.0 (−1.0 to 7.0)	0.173
(IQR)	T_1	69 (60, 74) (45, 85)	77 (68, 82) (51, 101)	MD, 8.0 (5.0 to 12.0)	< 0.001
(Min, Max)	T_2	70 (63, 76) (48, 87)	73 (69, 82) (60, 98)	MD, 5.0 (2.0 to 9.0)	0.003
beats per minute	T_3	71 (62, 77) (46, 102)	72 (65, 78) (52, 114)	MD, 2.0 (−1.0 to 6.0)	0.234
	T_4	68 (61, 76) (50, 106)	72 (65, 78) (50, 104)	MD, 4.0 (−1.0 to 8.0)	0.111
	T_5	61 (54, 68) (47, 79)	61 (57, 67) (45, 94)	MD, 1.0 (−2.0 to 4.0)	0.523
	T_6	70 (61, 75) (46, 96)	72 (66, 78) (56, 92)	MD, 3.0 (0 to 7.0)	0.040
MAP, median	T_0	90 (81, 99) (69, 129)	91 (84, 100) (70, 131)	MD, 1.0 (−3.0 to 6.0)	0.557
(IQR)	T_1	79 (72, 86) (64, 130)	88 (80, 95) (70, 120)	MD, 8.0 (4.0 to 13.0)	< 0.001
(Min, Max)	T_2	85 (77, 92) (63, 121)	92 (82, 104) (71, 164)	MD, 7.0 (3.0 to 12.0)	0.005
mmHg	T_3	83 (77, 90) (67, 114)	90 (83, 96) (72, 123)	MD, 7.0 (3.0 to 10.0)	< 0.001
	T_4	83 (79, 91) (68, 111)	88 (82, 93) (74, 122)	MD, 5.0 (1.0 to 8.0)	0.009
	T_5	87 (80, 93) (71, 118)	90 (86, 98) (70, 125)	MD, 5.0 (1.0 to 9.0)	0.013
	T_6	84 (78, 92) (68, 111)	85 (78, 92) (69, 125)	MD, 0 (−3.0 to 4.0)	0.986
SAP, median	T_0	123 (108, 136) (96, 190)	120 (112, 136) (90, 178)	MD, 1.0 (−6.0 to 8.0)	0.843
(IQR)	T_1	105 (98, 115) (87, 195)	115 (106, 126) (92, 168)	MD, 9.0 (4.0 to 15.0)	< 0.001
(Min, Max)	T_2	113 (103, 127) (84, 181)	119 (109, 138) (97, 182)	MD, 7.0 (1.0 to 14.0)	0.019
mmHg	T_3	113 (103, 120) (91, 151)	119 (109, 128) (95, 163)	MD, 6.0 (1.0 to 11.0)	0.021
	T_4	112 (107, 121) (96, 147)	115 (109, 128) (96, 172)	MD, 3.0 (−1.0 to 8.0)	0.136
	T_5	114 (106, 123) (96, 157)	121 (111, 131) (98, 182)	MD, 6.0 (1.0 to 11.0)	0.021
	T_6	112 (106, 124) (100, 154)	114 (106, 126) (88, 163)	MD, 0 (−5.0 to 5.0)	0.967
DAP, median	T_0	69 (65, 76) (49, 94)	73 (65, 78) (55, 104)	MD, 2.0 (−2.0 to 6.0)	0.267
(IQR)	T_1	61 (55, 69) (39, 91)	68 (62, 78) (47, 91)	MD, 8.0 (4.0 to 12.0)	< 0.001
(Min, Max)	T_2	66 (56, 73) (43, 97)	72 (63, 82) (51, 127)	MD, 7.5 (3.0 to 12.0)	0.003
mmHg	T_3	63 (58, 72) (53, 90)	72 (66, 77) (51, 99)	MD, 8.0 (4.0 to 11.0)	< 0.001
	T_4	68 (62, 72) (46, 87)	74 (66, 80) (56, 104)	MD, 5.0 (2.0 to 9.0)	0.002
	T_5	72 (66, 80) (51, 98)	76 (70, 84) (55, 108)	MD, 5.0 (1.0 to 8.0)	0.018
	T_6	70 (64, 77) (52, 93)	73 (65, 79) (50, 107)	MD, 0 (−3.0 to 4.0)	0.807
RR, median	T_0	18 (18, 19) (12, 29)	18 (18, 18) (12, 22)	MD, 0 (0 to 0)	0.792
(IQR)	T_1	15 (12, 18) (2, 26)	18 (15, 20) (10, 25)	MD, 2.0 (0 to 3.0)	0.012
(Min, Max)	T_2	15 (12, 18) (6, 21)	19 (16, 22) (10, 30)	MD, 4.0 (3.0 to 6.0)	< 0.001
breaths per minute	T_3	16 (14, 18) (8, 24)	19 (17, 20) (12, 31)	MD, 2.0 (1.0 to 4.0)	< 0.001
	T_4	18 (16, 18) (9, 22)	19 (18, 21) (14, 30)	MD, 2.0 (1.0 to 3.0)	< 0.001
	T_5	18 (17, 18) (10, 23)	18 (18, 19) (15, 23)	MD, 0 (0 to 0)	0.212
	T_6	18 (16, 18) (14, 20)	18 (18, 18) (16, 21)	MD, 0 (0 to 0)	0.301
SpO_2, median	T_0	99 (98, 100) (95, 100)	99 (98, 100) (96, 100)	MD, 0 (0 to 0)	0.507
(IQR)	T_1	100 (99, 100) (96, 100)	100 (99, 100) (95, 100)	MD, 0 (0 to 0)	0.368
(Min, Max)	T_2	99 (99, 100) (96, 100)	99 (99, 100) (96, 100)	MD, 0 (0 to 0)	0.892
%	T_3	99 (99, 100) (96, 100)	99 (99, 100) (97, 100)	MD, 0 (0 to 0)	0.629
	T_4	99 (100, 100) (98, 100)	99 (100, 100) (97, 100)	MD, 0 (0 to 0)	0.945
	T_5	100 (100, 100) (98, 100)	100 (100, 100) (98, 100)	MD, 0 (0 to 0)	0.972
	T_6	99 (98, 100) (95, 100)	99 (98, 100) (96, 100)	MD, 0 (0 to 0)	0.809

Notes: Data are presented as median (interquartile range) (minimum, maximum). T_0, time of 30 minutes before anesthesia induction; T_1, time of the MOAA/S scale score ≤ 1 after injecting propofol; T_2, time of cervical dilation using the largest cervical dilator; T_3, time of the end of the surgery; T_4, time of the MOAA/S scale score ≥ 4; T_5, time of leaving the PACU; T_6, time of discharge. A *P* value of < 0.05 was considered statistically significant.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; RR, respiratory rate; SpO2, pulse oxygen saturation; IQR, interquartile range; Min, minimum; Max, maximum; CI, confidence interval; MD, median difference.

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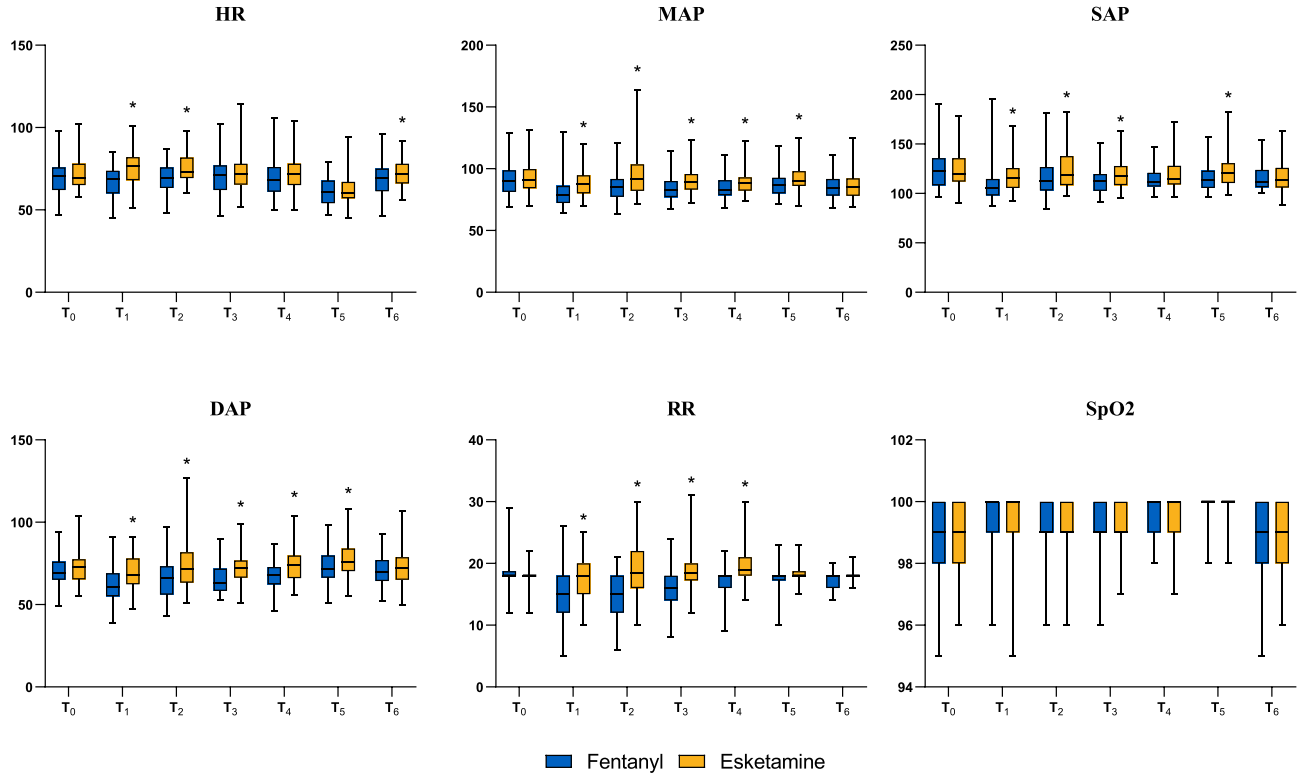

Figure 4 Perioperative trends in vital sign parameters.
Notes: The asterisk represents a significant between-group difference ($P < 0.05$).
Abbreviations: HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; RR, respiratory rate; SpO2, pulse oxygen saturation.

Adverse Reactions

Incidence rates of dizziness (0% vs 1.8%; RR, 2.0; 95% CI: 0.4–2.4; $P = 1.000$), hypertension (3.6% vs 7.1%; RR, 1.4; 95% CI: 0.6–2.0; $P = 0.679$), hypotension (3.6% vs 0%; RR, 0; 95% CI: 0–1.3; $P = 0.495$), tachycardia (1.8% vs 1.8%; RR, 1.0; 95% CI: 0.2–1.9; $P = 1.000$), and bradycardia (3.6% vs 10.7%; RR, 1.6; 95% CI: 0.8–2.2; $P = 0.271$) were comparable between groups. No headache, psychiatric symptoms, nausea, or vomiting were observed in either group. However, the incidence of respiratory depression was significantly lower in the esketamine group than in the fentanyl group (26.8% vs 3.6%; RR, 0.2; 95% CI: 0.06–0.6; $P = 0.001$) (Table 4).

Table 4 Comparison of the Adverse Events Between the Two Groups

Adverse Events	Fentanyl Group (n = 56)	Esketamine Group (n = 56)	Estimated Effects (95% CI)	*P* value
Headache	0 (0)	0 (0)	NA	NA
Dizziness	0 (0)	1 (1.8)	RR, 2.0 (0.4 to 2.4)	1.000
Hypertension	2 (3.6)	4 (7.1)	RR, 1.4 (0.6 to 2.0)	0.679
Hypotension	2 (3.6)	0 (0)	RR, 0 (0 to 1.3)	0.495
Tachycardia	1 (1.8)	1 (1.8)	RR, 1.0 (0.2 to 1.9)	1.000
Bradycardia	2 (3.6)	6 (10.7)	RR, 1.6 (0.8 to 2.2)	0.271
Respiratory depression	15 (26.8)	2 (3.6)	RR, 0.2 (0.06 to 0.6)	0.001
Psychiatric symptoms	0 (0)	0 (0)	NA	NA
Nausea	0 (0)	0 (0)	NA	NA
Vomiting	0 (0)	0 (0)	NA	NA

Notes: Data are presented as number of patients (%). A *P* value of < 0.05 was considered statistically significant.
Abbreviations: CI, confidence interval; RR, relative risk; NA, not applicable.

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Discussion

In this study, probit regression analysis was utilized to determine the ED90 values of esketamine (0.423 mg/kg) and fentanyl (1.424 μg/kg) in patients undergoing hysteroscopy. To our knowledge, this is the first report to establish the effective dose of fentanyl specifically for hysteroscopic procedures. The ED90 of esketamine obtained in our study was similar to the ED95 values (0.429 mg/kg) reported in previous literature on hysteroscopic surgery.[11] Furthermore, the combination of a subanesthetic dose of esketamine (< 0.5 mg/kg) with propofol demonstrates superior analgesic efficacy for various non-operating-room sedation procedures.[22] It is important to emphasize that a sample size of at least 60 patients is required to estimate the ED90 with moderate confidence, whereas calculating the ED95 would likely require more than 100 subjects.[13] Although earlier study have reported ED95 values (0.254 mg/kg), their sample sizes were below the recommended threshold even for ED50 estimation (n = 30), which may compromise the accuracy of their results.[12] Furthermore, the biased coin design applied in our current study may provide a more precise estimation of the ED compared to the conventional up-and-down method.[23] While targeting the ED95 could achieve adequate surgical conditions in a larger proportion of patients, the associated higher dose also increases the risk of adverse effects as it approaches or enters the dose range where side effects become significantly more probable.

Under the equipotent ED90 doses of esketamine and fentanyl, the incidence of physical movements during hysteroscopic surgery was 5% in both groups, indicating comparable efficacy in suppressing intraoperative movement. Compared to sulfentanyl, esketamine coadministered with propofol decreases propofol demand in hysteroscopic procedures.[24] Esketamine exhibits analgesic properties and synergizes with propofol via anti-nociceptive mechanisms, potentially lowering propofol demand. However, in the current study, no significant differences were found between groups regarding propofol usage—including total consumption, dosage, infusion rate, or administration frequency. This finding aligns with reports from studies using alfentanil, implying that at equivalent analgesic levels, esketamine does not confer an additional propofol-sparing benefit.[12] However, the comparable propofol usage between groups effectively eliminates this confounder, enabling a more valid comparison of respiratory and circulatory stability as well as adverse effects between the esketamine and fentanyl groups.

Our study demonstrated that patients in the esketamine group exhibited superior maintenance of hemodynamic parameters during hysteroscopic surgery. Specifically, esketamine effectively counteracted the hypotensive and bradycardic effects commonly associated with propofol and fentanyl. Esketamine's cardiovascular effects are thought to stem from inhibition of brainstem parasympathetic neurons and enhancement of sympathetic activity, leading to increased cardiac output and systemic vascular resistance.[25–27] These actions enable esketamine to counteract propofol-induced cardiovascular depression, a benefit particularly relevant in elderly patients.[28]

Propofol injection pain is one of the most common complaints during anesthesia induction, characterized by a burning sensation that radiates from the injection site along the entire arm. This phenomenon occurs as high concentrations of propofol directly irritate vascular nociceptors and surrounding free nerve endings and subsequently activate the plasma kallikrein-kinin system,[29,30] inducing widespread vascular pain. While various methods can alleviate this pain,[31] pretreatment with esketamine is an effective approach. Esketamine, with approximately twice the NMDA receptor affinity of racemic ketamine, reduces injection pain through local anesthetic and synergistic hypnotic effects,[32] as demonstrated by studies using 0.2 mg/kg to effectively alleviate propofol-induced pain.[33] Therefore, at doses effective in suppressing physical movements, it could concurrently alleviate this injection pain.

Compared to propofol alone, adding 0.25 mg/kg esketamine shortened induction and recovery times in 114 obese patients during gastroscopy.[34] Likewise, a subanesthetic esketamine-propofol combination significantly reduced recovery time versus an alfentanil-propofol regimen in hysteroscopy patients. This effect may be attributed to esketamine's activation of glutamatergic neurons in the paraventricular thalamus, which promotes awakening.[35] In terms of adverse effects, our study did not observe a significant increase in psychotomimetic symptoms with esketamine administration. Respiratory depression is a common and serious intraoperative adverse event, often associated with the use of opioids and high doses of propofol. Mild respiratory depression can often be managed by chin lift, while severe cases may require assisted ventilation or even tracheal intubation. These interventions can provoke patient movement, thereby interfering with surgical procedures. Esketamine's respiratory effects appear dose-dependent; while high doses may

depress respiration, clinically relevant doses tend to stimulate respiration and can reverse opioid-induced respiratory depression.[36–38] This respiratory stimulation likely involves multiple receptor-mediated pathways, including adrenergic and glutamatergic systems.[39] Our findings support this observation, indicating that patients in the esketamine group experienced fewer episodes of respiratory depression compared to those in the fentanyl group.

Patients undergoing hysteroscopic surgery often experience varying degrees of preoperative anxiety, which is frequently overlooked in clinical practice yet can negatively impact postoperative pain and recovery. This anxiety typically stems from fears related to the procedure itself and concerns about potential underlying conditions - especially when malignancy is suspected. In this study, the median preoperative HADS score was 6 in both groups, lower than the average score of 11.3 reported in cancer-screening populations,[40] likely because most participants were abortion patients who experienced less diagnosis-related psychological distress. Although HADS scores decreased in both groups at one month post-surgery, likely reflecting the resolution of procedure-related anxiety, the reduction was significantly greater in the esketamine group. In a single-center, double-blind, placebo-controlled randomized clinical trial, Qiu et al reported that the esketamine group showed a significantly reduced incidence of depressive symptoms on the first day after surgery compared to baseline.[41] Consistent with a previous systematic review,[42] esketamine was associated with short- and long-term improvement in postoperative anxiety, attributable both to the resolution of surgery-related concerns and to its intrinsic anxiolytic and antidepressant effects.

This study has several limitations. First, the sample size was calculated to detect a 20% reduction in propofol consumption; however, the observed between-group difference was smaller than anticipated. Post-hoc analysis revealed that the study was underpowered to detect this smaller effect size with statistical significance. This underpowering likely stems from an optimistic estimation of the treatment effect based on prior literature and the use of a standard deviation derived from retrospective data, which may not fully capture variability in a prospective trial setting. Therefore, the lack of a statistically significant difference should be interpreted with caution and does not exclude the possibility of a smaller yet clinically meaningful benefit of esketamine. Additionally, although 60 participants were initially planned for ED90 estimation, exclusions and dropouts reduced the final sample size, potentially compromising the accuracy of this estimate. Second, the clinical significance of the observed differences in HADS scores is unclear, as a change of less than 8 points may not reach the threshold of minimal clinical importance; thus, future studies should consider evaluating this outcome using multiple assessment tools. Finally, the single-center design limits generalizability, underscoring the need for validation in larger, multi-center trials. While rigorous blinding procedures were implemented, the distinct pharmacological profiles of the two drugs, particularly the sympathomimetic effects of esketamine, may have compromised blinding in some instances.

Conclusions

At equipotent ED90 doses, esketamine matches fentanyl's analgesic efficacy during hysteroscopy but demonstrates superior overall outcomes through enhanced safety, faster recovery, and potential psychological benefits, thereby establishing it as a preferable alternative. However, broader validation through multicenter studies and investigations in older patient populations is warranted before recommending widespread clinical adoption.

Abbreviations

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CONSORT, Consolidated Standards of Reporting Trials; DAP, diastolic arterial pressure; ED50, effective dose 50; ED90, effective dose 90; HADS, Hospital Anxiety and Depression Scale; HR, heart rate; IQR, interquartile range; MAP, mean arterial pressure; MD, median difference; MOAA/S, modified observer's assessment of alertness/sedation; NMDA, N-methyl-D-aspartate; NRS, Numerical rating scale; PACU, post-anesthesia care unit; RR, respiratory rate; RR, relative risk; SABCD, sequential allocation biased-coin design; SAP, systolic arterial pressure; SD, standard deviation; SpO_2, pulse oxygen saturation; WPS, Word Processing System.

Data Sharing Statements

Data are available from the corresponding author.

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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The authors have no competing interests to declare.

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