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CLINICAL TRIAL REPORT

# The Comparison of the Efficacy of Esketamine Over Sufentanil to Reduce Postoperative Nausea and Vomiting in Gynecological Laparoscopic Surgery: A Prospective, Double-Blind, Randomized Controlled Trial

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**Background:** Postoperative nausea and vomiting (PONV) affect 40–80% of patients undergoing gynecological laparoscopy (GLS). Opioids, though effective for analgesia, may exacerbate PONV. Esketamine, the dextrorotatory form of ketamine with analgesic, sedation and anti-inflammatory properties, was evaluated for PONV prophylaxis compared to sufentanil.

**Methods:** In this single-center, double-blind trial, 150 patients undergoing elective GLS were randomized to receive esketamine (0.25mg/kg, n=75) or sufentanil (0.1μg/kg, n=75) at the incision closing. Primary outcomes were PONV incidence and severity in Postanesthesia care unit (PACU) and during 48 hours postoperation. Secondary outcomes included pain scores, supplemental analgesia use, sore throat and bucking at excubation. Statistical analyses utilized t-tests, Mann–Whitney U, and $\chi^2$-tests (significance: $p < 0.05$) with Friedman test for within-group comparisons and generalized estimating equations (GEE) for group-time interaction evaluation.

**Results:** The esketamine group demonstrated significantly lower PONV incidence (in PACU: 57.3% vs 36%, p=0.014; 24h: 53.3% vs 36%, p=0.048) and reduced severity within 24 hours (in PACU, p<0.001; 6h, P=0.042; 24h, p=0.029). Secondary outcomes favored esketamine: lower dynamic pain scores during coughing (in PACU, p=0.017; 6h, P=0.021; 24h, p=0.012), lower severity of sore throat (6h, P=0.019; 24h, p=0.028), reduced rescue analgesia needs (6h: RD=0.12, p=0.037), and decreased incidence of bucking reflex (RD=0.21, p=0.014).

**Conclusion:** Single-dose esketamine significantly reduces PONV incidence and severity in GLS, improves dynamic analgesia, and mitigates extubation complications. These results support the single dose use of esketamine as an opioid-sparing adjunct to prevent PONV in gynecological laparoscopy.

**Keywords:** postoperative nausea and vomiting, esketamine, gynecological laparoscopy, general anesthesia, opioids

## Introduction

Postoperative nausea and vomiting (PONV) represent a major source of postoperative distress, affecting 40–60% of surgical patients and contributing to serious complications including aspiration pneumonia, wound dehiscence, and prolonged hospitalization.[1] Female gender, recognized as an independent risk factor of PONV,[2,3] synergizing with surgical characteristics and perioperative psychological stressors such as preoperative anxiety and sleep disturbances,[4–6] are to aggravate the degree of postoperative nausea and vomiting in gynecological laparoscopy (GLS). Previous clinical trials

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reported the incidence rates of PONV in patients received GLS could raise up to 60–80%.[2,3] Consequently, it is imperative to mitigate the risk of PONV in gynecological laparoscopy.[7,8]

Contemporary PONV prophylaxis strategies emphasize multimodal approaches combining 5-hydroxytryptamine receptor antagonists,[9] corticosteroid,[10] pyridoxine,[3] and, especially opioid-sparing protocols.[11,12] While opioid minimization demonstrates particular efficacy through releasing nausea pathways and reducing gastric retention, complete opioid elimination remains constrained by technical demands of regional anesthesia and limitations in anesthesia and analgesic effect.[1,13] This therapeutic gap underscores the need for accessible opioid-adjuvant agents with adequate analgesic properties and mild gastrointestinal reaction.

Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist valued for its rapid recovery profile and favorable analgesic properties, has gained widespread application in pediatric and short-duration surgical procedures. Recent pharmacological developments have introduced esketamine, the dextrorotatory enantiomer of ketamine with a higher affinity for NMDA receptors, which demonstrates enhanced clinical efficacy in analgesic and antidepressant effects.[14] Previous studies indicate that esketamine exhibits three-fold greater analgesic potency and 1.5-fold higher anesthetic efficacy compared to the racemic ketamine formulation. When used for postoperative analgesia, esketamine improves analgesia and reduces opioid consumption;[4,8] but, data of improvement in PONV by esketamine are limited.[12] The present trial aims to examine whether a single analgesic dose use of esketamine reduces the incidence of PONV in patients receiving GA for gynecological laparoscopic surgery.

# Materials and Methods

## Ethical Approval and Trial Registration

This prospective, double-blind, single-center, randomized controlled trial was approved by the Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (TAH-SYSU) (Approval No. [2023-169-02]) and registered in the Chinese Clinical Trial Registry (ChiCTR2300075533). All participants provided written informed consent. The study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the principles of the Declaration of Helsinki.

## Patients

This study was conducted from April 2023 to July 2024. Hospitalized patients in the TAH-SYSU scheduled for elective general anesthesia laparoscopic gynecological surgery with an anticipated duration >2 hours were screened for eligibility. The age range of eligible participants was 18–60 years old, and the American Society of Anesthesiologists (ASA) physical status classification was limited to grades I–II. The patients' body mass index (BMI) is calculated by dividing the weight (Unit: Kilogram) by the square of the height (Unit: Meter). Those who had a Mallampati score of IV, psychotropic medication usage within 3 days preoperatively, requirement for abdominal lymph node dissection, reintubation, postoperative aspiration, known or predicted difficult airway, or contraindications to esketamine were excluded. Patients with Cormack Lehane grade III or IV laryngoscopic view, contraindications to ketamine or esketamine, requirement for postoperative mechanical ventilation, or intraoperative conversion to laparotomy were also excluded.

## Randomization and Blinding

Participants were randomly allocated (1:1 ratio) to the esketamine (Esk) or sufentanil control (Con) group using computer-generated randomization lists (Excel 2023, Microsoft) sealed in opaque, sequentially numbered envelopes. To mitigate bias from esketamine-related adverse events, group assignments were disclosed only to the administering anesthesiologist, while outcome assessors and data collectors remained blinded throughout the study.

## Intervention

No premedication was subjected to the participants. Non-invasive and invasive blood pressure measurement (including the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)), heart rate (HR), electrocardiography, pulse oximetry, and the Narcotrend Index monitoring (MT MonitorTechnik GmbH & Co., KG, Germany) were

performed preinduction. The anesthesia process commenced with a single dose of 0.3μg/kg dexmedetomidine administered to alleviate the patient's anxiety. For induction, propofol was first administered by TCI (Alaris Medical Systems, Inc., San Diego, CA, USA) based on the Marsh model with a target plasma concentration of 4μg/mL. With the onset of the patient's unconsciousness, remifentanil was administered by TCI based on the Minto model with a target plasma concentration of 4ng/mL. Loss of eyelash reflex was assessed every 10 seconds. Single dose medications used to induce GA including 5mg dexamethasone, 0.5μg/kg sufentanil and 0.2mg/kg cisatracurium. Muscle relaxation was assessed every 10s using a "train of four" (neuromuscular transmission) monitor (Mindray Bio-Medical Electronics, China). The endotracheal tube intubation was performed by an independent qualified anesthesiologist who was unaware of the patient's group assignment. Tube size was selected based on the preoperative computed tomography-measured bronchial width of each patient. Tracheal tube cuff pressure will be maintained at 20–35 cm H2O to minimize mucosal injury.

GA was maintained through 2μg/mL propofol (TCI based on the Marsh model and adjusted according to the Narcotrend Index), 4 ng/mL remifentanil (TCI based on the Minto model and adjusted according to the blood pressure and electrocardiography) plus cisatracurium (1μg/kg per min).

Concurrently, patients were monitored for changes in blood pressure outside ±20% from baseline. In this study, we determined the baseline blood pressure as the average of the blood pressure measured at the preoperative evaluation clinic (measured on either arm with the patient in the sitting position) and all available blood pressure measurements in the operating room before the administration of induction medication. The tidal volume was set at 4–6 mL/kg during the GA period, and other ventilator parameters were adjusted to the peak inspiratory pressure of < 30cmH2O and end tidal CO2 of < 45mmHg.

At the start of incision suturing, patients were intravenously injected with tropisetron (5mg) and neostigmine (0.05mg/kg) plus atropine (0.02mg/kg) to antagonise the residual neuromuscular block. To alleviate postoperative pain, the surgeon performed wound infiltration with 0.375% ropivacaine. During the suture of skin incision, esketamine 0.25mg /kg or sufentanil 0.1μg/kg was given intravenously according to the random number grouping. After the resuscitation and extubation, a single dose of esketamine 0.1mg/kg was added when VAS>4 in the Esk Group, and 0.04μg/kg sufentanil was injected when VAS >4 in the Con Group.

## Sample Size Calculation

In a previous study, PONV occurred in 60% of patients within the first 24 h of gynecological laparoscopy.[15,16] An approximately 40% reduction in the incidence of PONV was showed in our preliminary experiment and regarded as clinically significant. Thus, a sample size of 65 participants per group would be needed to achieve a power of 0.8 and a risk of 0.05 for type-I errors in two-tailed statistical analyses. Considering the potential for loss of follow-up or consent withdrawals, a total of 75 patients were included in each group for this trial.

## Outcomes

The primary outcomes included the incidence and severity of PONV within 48 h after surgery. Secondary outcomes included the postoperative extubation time, degree of bucking at excubation and pharyngalgia after excubation, proportion of additional analgesia in post-anesthesia care unit (PACU), pain scores in rest condition and at cough evaluated by an 0–10 point VAS.

## Outcome Assessments and Data Collection

The degree of anxiety and depression was evaluated by Beck's anxiety and depression self-rating scale. A 0–3 degree was used to evaluate the severity of postoperative nausea and vomiting (0: no; 1: mild or only nausea; 2: medium or retching; 3: severe vomiting). Patients were assessed for PONV, analgesic requirements and VAS pain-scores at four time points within 48 h: at the PACU, at a first study visit (V1) six hours post-operative (PO), a second visit (V2) 24 hours PO, and a third visit (V3) two days after surgery. This validated interview consists of two questions (Q1. Have you experienced a discomfort feeling of nausea?; Q2. Have you vomited or had dry retching?) to define clinically PONV. Data on medical history, surgery and usage of analgesic or antinausea drug were extracted from the medical record.

## Statistical Analysis

Continuous variables were assessed for normality using Shapiro–Wilk tests. Continuous variables were compared using independent t-tests and presented with mean±standard deviation (SD) +95% confidence interval (CI). Nonparametric data (PONV/pain scores) and ordinal outcomes (eg, severity scores) were analyzed between groups at each time point using Mann–Whitney tests and indicated as median (interquartile, [range]) with median differences (MD) and 95% confidence interval (CI). For within-group comparisons across multiple time points, the Friedman test was used, followed by post-hoc pairwise comparisons with Bonferroni adjustment. Additionally, Rank-Biserial correlation, average rank statistics and generalized estimating equations (GEE) models were employed for non-normally distributed and ordinal outcomes to evaluate the group–time interaction. The severity outcome (Severity of PONV and VAS of Pain) was dichotomized a priori using a threshold of ≥1 versus 0, based on clinical relevance indicating the presence versus absence of any measurable severity. A GEE model with a binomial family and logit link function was then fitted using the geeglm function, assuming an exchangeable working correlation structure. The model included the following covariates: Age, BMI, Duration of Anesthesia, and ASA grade. Covariates included Age, BMI, Duration of Anesthesia, and ASA grade. Categorical data (counts/%) were assessed by $\chi^2$/Fisher's exact tests, with rate differences (RD) + 95% CI calculated via Wilson method. To assess potential confounding effects of baseline covariates, linear regression was performed for continuous outcomes with adjustment for relevant variables. Analyses used GraphPad Prism 10.8 (GraphPad Software., San Diego, CA, USA) and R version 4.4.1 (for Rank-Biserial correlation, average rank statistics and GEE models), with significance at $p<0.05$. There were no missing data in the primary outcomes (incidence and severity of PONV, pain scores, sore throat, and bucking). For the small amount of missing baseline data, we employed Multiple Imputation by Chained Equations (MICE) using the mice package in R with m=5 imputed datasets. The imputation model incorporated all available demographic variables, baseline data, and all outcome variables to ensure proper compatibility and valid inferences. The results from the multiple imputations were pooled using Rubin's rules.

# Result

## Patient Characteristics

A total of 173 patients were enrolled, with 159 proceeding to primary randomization. Fourteen patients were excluded preoperatively: ten due to unwillingness to complete preoperative assessment scales, three due to consent withdrawal, two for psychotropic medication use, and one for severe cephalalgia. Postoperatively, nine additional patients were excluded: seven owing to conversion to laparotomy and two for secondary surgical intervention (Figure 1). No patients in the sufentanil group received esketamine, ketamine, or other NMDA receptor antagonists during induction or surgery. Demographic and baseline clinical characteristics were comparable between groups (Table 1). The GLS were performed among the most common surgical procedures. Surgical duration and total anesthesia time showed no intergroup differences; however, time to extubation was shorter in the Esk group (Con 21.1±9.0 versus Esk 17.9±8.3, P=0.029) (Table 1). Sensitivity analyses via regression models confirmed that baseline differences did not significantly alter the primary findings (Supplementary Table S1).

## Primary Outcomes

As shown in Tables 2 and 3, compared to the Con group, the Esk group exhibited significantly reduced PONV severity in the PACU (MD, −1.00; 95% CI, −1.00 to 0.00, P<0.001), V1 (6h PO, MD, 0.00; 95% CI, −1.00 to 0.00, P=0.042) and V2 (24h PO, MD, −1.00; 95% CI, 0.00 to 0.00, P=0.029). No significant reduction was observed at V3 (48h PO, MD, 0.0; 95% CI, 0.00 to 0.00, P=0.990) (Table 2 and Figure 2A). Similarly, PONV incidence was lower in the Esk group during PACU stay (RD, 0.213; 95% CI, 0.044 to 0.367, P=0. 014), at V1 (RD, 0.200; 95% CI, 0.034 to 0.352, P=0.019) and at V2 (RD, 0.173; 95% CI, 0.005 to 0.329, P=0.048) with no intergroup difference at V3 (RD, 0.040; 95% CI, −0.083 to 0.163, P=0.639) (Table 3). Friedman tests confirmed significant temporal reductions in PONV severity in both groups (Con: $\chi^2$=57.55, p<0.001; Esk: $\chi^2$=21.34, p<0.001, Supplementary Table S2), with post hoc analyses indicating steep declines from PACU to 48h (Supplementary Table S3). GEE models validated esketamine's superior efficacy on PONV severity (group effect: estimate=−1.268, P<0.001; time effect: V1: P=0.259, V2: P=0.509; group–time interaction: V1:

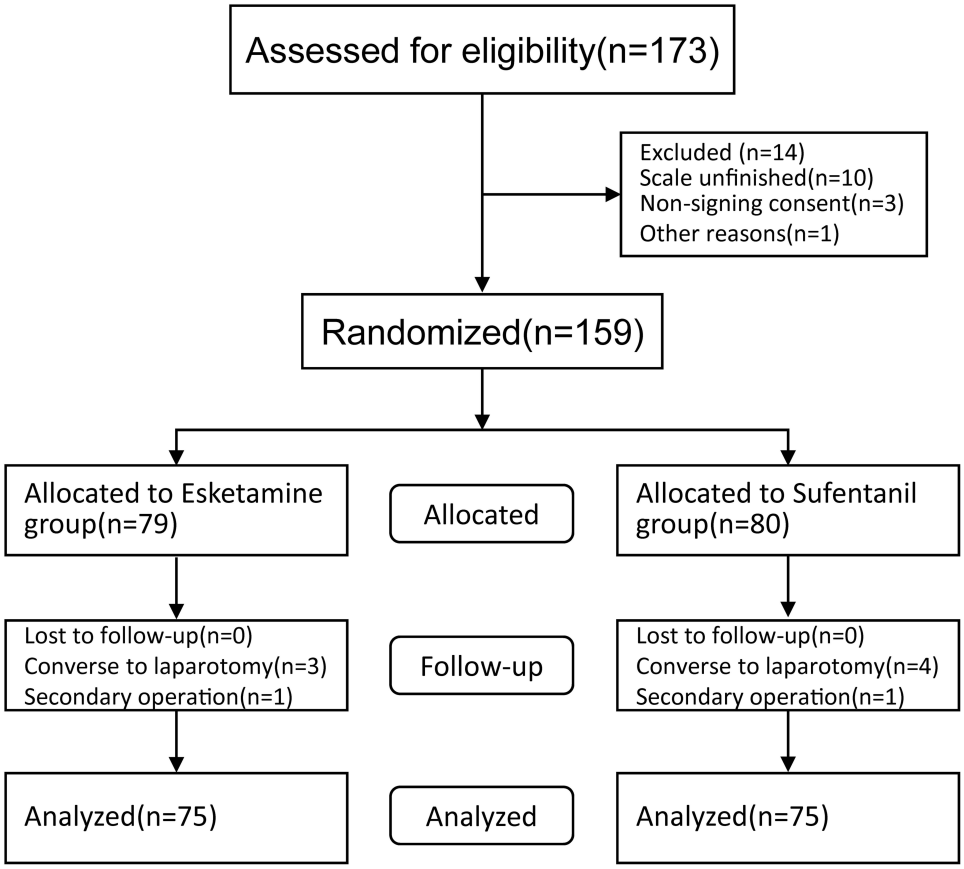


**Figure 1** Study flow diagram.

P=0.818, V2: P=0.449, Supplementary Table S4) and incidence (group effect: estimate=−1.151, P<0.001; time effect: V1: P=0.385, V2: P=0.186; group–time interaction: V1: P=0.537, V2: P=0.354, Supplementary Table S5) within 24h post-operation.

**Table 1** Demographics, Baseline Data, and Procedure Time

| Characteristic | Con (n=75) | Esk (n =75) | P value |
|---|---|---|---|
| Age, mean±SD, year | 32.8±7.9 | 33.1±9.2 | 0.811 |
| Height, mean±SD, cm | 159.3±5.2 | 158.8±3.5 | 0.544 |
| Weight, mean±SD, kg | 55.9±9.1 | 53.3±8.3 | 0.063 |
| BMI, mean±SD | 22.1±3.8 | 21.2±3.6 | 0.130 |
| ASA status patient number (%) | | | |
| I | 64 (85.3) | 62 (82.7) | >0.999 |
| II | 11 (14.7) | 13 (17.3) | |
| Surgical history patient number (%) | | | |
| Yes | 21 (28.0) | 23 (30.7) | 0.859 |
| No | 54 (72.0) | 52 (69.3) | |
| Current smoker patient number (%) | | | |
| Yes | 2 (2.7) | 1 (1.3) | >0.999 |
| No | 73 (97.3) | 74 (98.7) | |

(*Continued*)


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**Table 1** (Continued).

| Characteristic | Con (n=75) | Esk (n =75) | P value |
|---|---|---|---|
| Baseline measurements | | | |
| SBP, median (interquartile), mm Hg | 121 (112–126) | 120 (112–129) | 0.741 |
| DBP, median (interquartile), mm Hg | 71 (65–78) | 71 (67–77) | 0.921 |
| MAP, median (interquartile), mm Hg | 87 (82–93) | 88 (83–92) | 0.823 |
| HR, median (interquartile), bpm | 80 (74–85) | 78 (70–86) | 0.738 |
| Duration of anesthesia, mean±SD, min | 133.1±46.6 | 143.4±49.9 | 0.193 |
| Duration of artificial airway, mean±SD, min | 154.1±49.8 | 148.2±44.8 | 0.447 |
| Duration before extubation, mean±SD, min | 21.1±9.0 | 17.9±8.3 | 0.029 |
| Bleeding in operation, mean±SD, mL | 29.0±21.9 | 31.9±20.1 | 0.405 |

**Table 2** Trial Outcomes (Severity of PONV, Pain, Bucking, and Sore Throat)

| Variables | Con (n=75) | Esk (n=75) | MD (95% CI) | Rank-Biserial Correlation (95% CI) | P value |
|---|---|---|---|---|---|
| **Severity of PONV** | | | | | |
| PACU | 1.0 (0.0–1.0, [0.0–2.0]) | 0.0 (0.0–1.0, [0.0–2.0]) | −1.00 (−1.00 to 0.00) | 0.31 (0.14, 0.47) | <0.001 |
| V1 (6h) | 1.0 (0.0–1.0, [0.0–2.0]) | 1.0 (0.0–1.0, [0.0–3.0]) | 0.00 (−1.00 to 0.00) | 0.21 (0.02, 0.37) | 0.042 |
| V2 (24h) | 1.0 (0.0–1.0, [0.0–2.0]) | 0.0 (0.0–1.0, [0.0–3.0]) | −1.00 (0.00 to 0.00) | 0.20 (0.02, 0.37) | 0.029 |
| V3 (48h) | 0.0 (0.0–0.0, [0.0–1.0]) | 0.0 (0.0–0.0, [0.0–1.0]) | 0.00 (0.00 to 0.00) | −0.04 (−0.22, 0.14) | 0.990 |
| Friedman $\chi^2$ | 57.55 | 21.34 | | | |
| P-value | <0.001 | <0.001 | | | |
| **VAS of Pain (Rest)** | | | | | |
| PACU | 2.0 (1.0–2.0, [0.0–7.0]) | 2.0 (1.0–2.0, [0.0–4.0]) | 0.00 (0.00 to 0.00) | 0.07 (−0.11, 0.25) | 0.270 |
| V1 (6h) | 2.0 (1.0–2.0, [0.0–5.0]) | 1.0 (1.0–2.0, [0.0–4.0]) | −1.00 (−1.00 to 0.00) | 0.19 (0.00, 0.36) | 0.046 |
| V2 (24h) | 1.0 (1.0–2.0, [0.0–5.0]) | 1.0 (1.0–2.0, [0.0–6.0]) | 0.00 (−1.00 to 0.00) | 0.12 (−0.07, 0.29) | 0.148 |
| V3 (48h) | 1.0 (0.0–2.0, [0.0–3.0]) | 1.0 (0.0–2.0, [0.0–3.0]) | 0.00 (0.00 to 0.00) | 0.06 (−0.12, 0.24) | 0.476 |
| Friedman $\chi^2$ | 30.41 | 26.48 | | | |
| P-value | <0.001 | <0.001 | | | |
| **VAS of Pain (Cough)** | | | | | |
| PACU | 3.0 (2.0–4.0, [0.0–7.0]) | 2.0 (1.0–3.0, [0.0–5.0]) | −1.00 (−1.00 to 0.00) | 0.20 (0.02, 0.37) | 0.017 |
| V1 (6h) | 3.0 (2.0–3.0, [0.0–5.0]) | 2.0 (1.0–3.0, [0.0–5.0]) | −1.00 (−1.00 to 0.00) | 0.22 (0.04, 0.39) | 0.021 |
| V2 (24h) | 2.0 (1.0–3.0, [0.0–5.0]) | 2.0 (1.0–3.0, [0.0–5.0]) | 0.00 (−1.00 to 0.00) | 0.22 (0.04, 0.39) | 0.012 |
| V3 (48h) | 1.0 (0.0–3.0, [0.0–3.0]) | 2.0 (1.0–3.0, [0.0–3.0]) | 1.00 (0.00 to 1.00) | −0.08 (−0.26, 0.10) | 0.548 |
| Friedman $\chi^2$ | 50.84 | 18.49 | | | |
| P-value | <0.001 | <0.001 | | | |
| **Severity of Bucking** | | | | | |
| Extubation | 1.0 (0.0–1.0, [0.0–2.0]) | 0.0 (0.0–1.0, [0.0–2.0]) | −1.00 (0.00 to 0.00) | 0.21 (0.03, 0.38) | 0.013 |
| **Severity of Sore Throat** | | | | | |
| PACU | 1.0 (0.0–1.0, [0.0–3.0]) | 1.0 (0.0–1.0, [0.0–2.0]) | 0.00 (0.00 to 0.00) | 0.06 (−0.13, 0.24) | 0.270 |
| V1 (6h) | 2.0 (1.0–2.0, [1.0–3.0]) | 1.0 (1.0–2.0, [1.0–2.0]) | −1.00 (0.00 to 0.00) | 0.18 (−0.01, 0.35) | 0.019 |
| V2 (24h) | 2.0 (1.0–2.0, [1.0–4.0]) | 1.0 (1.0–2.0, [1.0–2.0]) | 0.00 (0.00 to 0.00) | 0.17 (−0.02, 0.34) | 0.028 |
| V3 (48h) | 1.0 (1.0–1.0, [1.0–3.0]) | 1.0 (1.0–1.0, [1.0–3.0]) | 0.00 (0.00 to 0.00) | 0.03 (−0.16, 0.21) | 0.679 |
| Friedman $\chi^2$ | 131.5 | 138.2 | | | |
| P-value | <0.001 | <0.001 | | | |

**Note**: Rank-Biserial Correlations were estimated using "effectsize" R-package.

**Table 3** Trial Outcomes (Incidence of PONV, Pain, and Bucking)

| Variables | Con (n=75) | Esk (n=75) | RD (95% CI) | P value |
|---|---|---|---|---|
| **Incidence of PONV** | | | | |
| PACU | 43 (57.3%) | 27 (36.0%) | 0.213 (0.044 to 0.367) | 0.014 |
| V1 (6h) | 53 (70.7%) | 38 (50.7%) | 0.200 (0.034 to 0.352) | 0.019 |
| V2 (24h) | 40 (53.3%) | 27 (36.0%) | 0.173 (0.005 to 0.329) | 0.048 |
| V3 (48h) | 9 (12.0%) | 12 (16.0%) | 0.040 (−0.083 to 0.163) | 0.639 |
| **Need of analgesics** | | | | |
| PACU | 19 (25.3%) | 16 (18.7%) | 0.04 (−0.104 to 0.183) | 0.404 |
| V1 (6h) | 13 (17.3%) | 4 (5.3%) | 0.12 (0.007 to 0.234) | 0.037 |
| **Incidence of Bucking** | | | | |
| At Extubation | 46 (61.3%) | 30 (40.0%) | 0.21 (0.044 to 0.367) | 0.014 |

## Secondary Outcomes

For the secondary outcomes, esketamine administration significantly reduced cough-associated wound pain in PACU (MD, −1.00; 95% CI, −1.00 to 0.00, P=0.017), at V1 (MD, - MD, −1.00; 95% CI, −1.00 to 0.00, P=0.021) and at V2 (MD, 0.00;

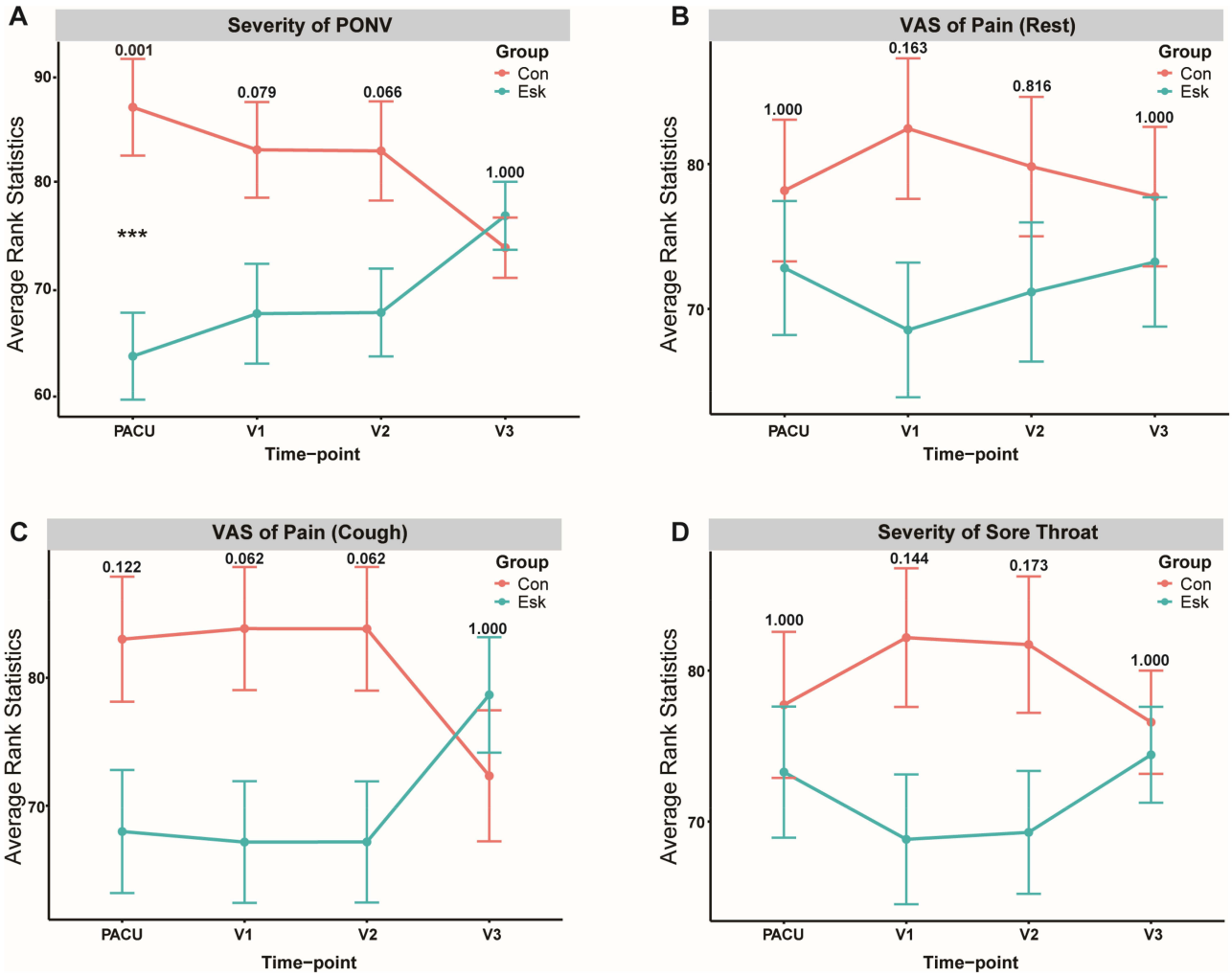


**Figure 2** Average Rank Statistics at each time point of PONV, Pain Score, and Sore throat. Marginal means of different time points based on average rank statistics. (**A**) Average Rank of Severity of PONV; (**B**) Average Rank of VAS of Pain (Rest); (**C**) Average Rank of VAS of Pain (Cough); (**D**) Average Rank of Severity of sore throat. Error bar reflected standard error. Bonferroni-adjusted post-hoc P-values and stars (***P<0.001) were showed in the figure.


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95% CI, −1.00 to 0.00, P=0.012) while no significant difference shown at V3 (MD, 1.00; 95% CI, 0.00 to 1.00, P=0.548). However, resting pain scores differed significantly only at V1 (MD, −1.00; 95% CI, −1.00 to 0.00, P=0.046) (Table 2 and Figure 2B–D). The Esk group required fewer supplemental analgesics at V1 (RD, 0.12; 95% CI, 0.007 to 0.234, P=0.037) (Table 3). Additionally, esketamine reduced both severity (MD, −1.00; 95% CI, 0.00 to 0.00, P=0.013) (Table 2) and incidence (RD, 0.21; 95% CI, 0.044 to 0.367, P=0.014) (Table 3) of bucking reflex during extubation. Sore throat severity was also lower in the Esk group at V1 (MD, −1.00; 95% CI, 0.00 to 0.00, P=0.019) and V2 (MD, 0.00; 95% CI, 0.00 to 0.00, P=0.028) (Table 2). Friedman tests revealed significant temporal improvements in VAS outcomes (both groups p<0.001; Supplementary Table S2), while GEE confirmed no time effect and group–time interact within 24h post-operation (Supplementary Tables S4 and S5).

## Discussion

In this single-center, double-blind, randomized controlled trial, we evaluated the preventive efficacy of single-dose esketamine versus sufentanil for postoperative nausea and vomiting (PONV) in patients undergoing elective gynecologic laparoscopic surgery under general anesthesia. The key findings of this study are threefold. First, the esketamine group demonstrated a clinically meaningful reduction in both the incidence and severity of PONV compared to the control group, suggesting that perioperative esketamine administration may serve as an effective prophylactic strategy for nausea and vomiting in this surgical cohort. Second, although resting pain scores assessed via VAS did not differ significantly between groups, patients receiving esketamine reported lower dynamic pain scores during coughing in the PACU and over the first 24 hours postoperatively. This was accompanied by a reduced requirement for rescue analgesics, indicating superior analgesic efficacy of esketamine in the acute postoperative period. Third, esketamine administration was associated with a decreased incidence of bucking reflex and pharyngeal discomfort following tracheal extubation, highlighting its potential role in mitigating emergence-related airway complications.

Opioids exert their analgesic effects through activation of peripheral and central nervous system opioid receptors[17,18] and are routinely administered intraoperatively to modulate surgical stress responses.[19,20] However, opioid-based postoperative analgesia is frequently complicated by adverse effects such as PONV,[19] cough,[21,22] and delayed excubation.[23] Notably, PONV incidence in patients undergoing gynecologic laparoscopy remains alarmingly high, with reported rates of up to 60%[7,16] —a finding consistent with the 57.3% incidence observed in our control group during PACU recovery. Current evidence suggests that opioid-sparing strategies may reduce PONV risk.[12] In this trial, esketamine reduced PONV incidence from 70.7% to 50.7% at the first postoperative assessment (V1) and from 53.3% to 36.0% at the second assessment (V2). Furthermore, the severity of PONV, quantified using a standardized 0–3 scale (0, no discomfort; 1, mild nausea; 2, retching and 3, severe vomiting), was significantly attenuated in the esketamine group throughout the 24-hour postoperative period. These findings collectively support the prophylactic utility of perioperative esketamine in mitigating PONV. In addition, the interval time between the ending of anesthetic drugs infusion and extubation was shorter in the esketamine group, demonstrating potential ability of esketamine to promote postoperative recovery via limiting opioid use.[24] This approach would offer a simple and easily implementable strategy with significant potential for widespread adoption, representing clinically relevant advances. Our findings also empower anesthesiologists to reduce PONV at a decisive moment. Nevertheless, further evidence from randomized controlled studies is needed to confirm this advantage.

Pharyngeal discomfort and tracheal extubation-related cough are recognized contributors to PONV.[25] Opioid-induced bucking reflex, a common complication during emergence,[21] may exacerbate pharyngeal irritation and subsequent nausea.[22,26] In our study, esketamine significantly reduced both the incidence and severity of bucking reflex compared to sufentanil, with concomitant improvements in patient-reported pharyngeal discomfort. This suggests that esketamine's ability to attenuate airway reflexes may indirectly contribute to its antiemetic effects by minimizing mechanical triggers for nausea, such as tracheal irritation.

Inadequate postoperative analgesia represents another key risk factor for PONV.[27,28] Severe pain may induce autonomic dysfunction[29] and stimulate serotonin release in the gastrointestinal tract,[30,31] mechanisms that could synergistically promote nausea and vomiting. While resting pain scores did not differ between groups, the esketamine group exhibited superior dynamic pain control during cough and reduced supplemental analgesic requirements. This enhanced analgesia of esketamine, achieved without increasing opioid consumption, likely contributed to the observed reduction in PONV. However, the

relationship between opioid consumption and PONV incidence remains complex, needing further evidence from basic research on pain pathways and vomiting mechanisms.

Beyond its analgesic properties, subanesthetic-dose esketamine has demonstrated ancillary benefits, including prevention of perioperative depressive symptoms, sleep disturbances, and delirium.[4,8,32] The precise mechanisms underlying its antiemetic effects remain unclear but may involve anti-inflammatory pathways.[33,34] Surgical trauma induces systemic inflammation, endothelial dysfunction, and neutrophil activation—processes implicated in postoperative gastrointestinal dysfunction.[35] Esketamine could thus contribute to its prophylactic effect on PONV through its ability to modulate inflammatory cascades. Nevertheless, further investigation is warranted to delineate whether these effects are mediated through opioid receptor antagonism or other molecular pathways.

This study has some limitations. First, due to the relatively young age of the patients underwent GLS in our center, the study may not present broad population characteristics of age, ASA grade and chronic disease. Second, this trial was conducted in a single center, and thus multicenter studies with a large sample size are needed. Third, biological samples, such as blood and feces, were not collected; these samples could have helped determine the possible mechanism behind the beneficial effect of esketamine on PONV markers in serum. Furthermore, due to the poor compliance of filling in the relevant scales, the improvement of anxiety and depression of patients perioperatively were not compared.

## Conclusions

The results of this double-blind, randomized controlled trial revealed that single dose esketamine infusion attenuated the PONV in patients who underwent gynecological laparoscopic surgery, both in incidence and severity. These findings hold broader clinical relevance by demonstrating a viable alternative to opioid-centric analgesia in gynecological laparoscopy, potentially reducing PONV-related complications and improving recovery quality. Further studies with a larger sample size are needed to confirm the prophylactic effect of esketamine on PONV.

## Data Sharing Statement

The data that support the findings of this study are available from the authors upon reasonable request.

## Ethics

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving human.

## Informed Consent and Patient Details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s). The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

## 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 declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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