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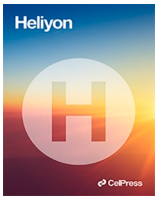

Research article

Effect of esketamine-based opioid-sparing anesthesia strategy on postoperative pain and recovery quality in patients undergoing total laparoscopic hysterectomy: A randomized controlled trail

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ABSTRACT

Objective: Opioid-sparing anesthesia reduces intraoperative use of opioids and postoperative adverse reactions. The current study investigated the effect of esketamine-based opioid-sparing anesthesia on total laparoscopic hysterectomy patients' recovery.

Methods: Ninety patients undergoing total laparoscopic hysterectomy were randomly assigned to esketamine-based group (group K) or opioid-based group (group C). The allocation to groups was unknown to patients, surgeons, and postoperative medical staff. The inability to implement blinding for anesthesiologists was due to the distinct procedures followed by the various groups while administering drugs. The QoR-40 and VAS were used to measure recovery quality. Postoperative adverse events, perioperative opioid consumption, and intraoperative hemodynamics were secondary endpoints.

Results: There was an absence of notable discrepancy in the baseline data observed between the two groups. The QoR-40 scores exhibited greater values in group K when compared to group C on the first day following the surgical procedure (160.91 ± 9.11 vs 151.47 ± 8.35, respectively; mean difference 9.44 [95 %CI: 5.78–13.11]; $P < 0.01$). Within 24 h of surgery, the VAS score of group K was lower at rest and during movement. ($P < 0.05$ for each). Group K had much lower rates of nausea and vomiting within 24 h of surgery. ($P < 0.05$ for each). Group K received significantly lower total doses of sufentanil and remifentanil than group C. (17.28 ± 2.59 vs 43.43 ± 3.52; 0.51 ± 0.15 vs 1.24 ± 0.24). The proportion of patients who used ephedrine in surgery was higher in group C than in group K ($P < 0.05$).

Conclusions: Esketamine-based opioid-sparing anesthesia strategy is feasible and enhanced recuperation following surgery by decreasing adverse effects associated with opioids and pain scores compared to an opioid-based anesthetic regimen.

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1. Introduction

In recent years, the majority of hysterectomy surgeries have been performed laparoscopically. The common consensus is that laparoscopic surgery is less traumatic, more aesthetic, and less painful than conventional laparotomy, resulting in faster recovery and shorter hospitalization [1,2]. Despite the fact that laparoscopy is less intrusive, discomfort from the pneumoperitoneum, placement of the trocars, and the length of the procedure nevertheless cause stress responses. Opioids, a potent analgesic, are fundamental components of classic balanced anesthesia [3,4].

Notably, perioperative administration of opioids is also linked to a number of detrimental side effects. The adoption of intraoperative opioid-sparing strategies, in which utilizing both non-opioid and opioid drugs in combination to enhance surgical outcomes, has been encouraged further by a deeper understanding of the detrimental effects on patient rehabilitation of opioid-related adverse effects [5–9]. Despite extensive research into Opioid-sparing anesthesia strategies for reducing surgical stimulation and opioid utilization, a sizable proportion of patients still experience unmanaged postoperative pain. The use of "adjuvants" judiciously can help to speed up recovery. In terms of anti-nociceptive management, multidrug regimens are believed to be more comprehensive since they particularly diminish sympathetic system activation by focusing on several routes and sites, including N-Methyl-D-Aspartate receptors (NMDA) [10–12].

Ketamine and esketamine are the two most commonly administered perioperative NMDA receptor antagonists since numerous clinical experiments have been conducted to test their analgesic properties [13]. However, esketamine, a ketamine isomer, is purported to possess greater potency and a reduced occurrence of unfavorable occurrences compared to racemic ketamine [14–16]. Esketamine has the capability to diminish the activation of N-Methyl-D-Aspartate receptors. It can also reduce central sensitization related to hyperalgesia, opioid tolerance, and chronic pain [17]. Despite the fact that NMDA receptors are involved in esketamine's primary mechanism of action, studies have also proven its capability to influence opioid receptors. It is thought that the interaction of released endogenous opioids and NMDA with these receptors can enhance the anti-nociception capability. In addition, the perioperative use of esketamine can also lessen the inflammatory response following surgery and resist respiratory depression caused by opioids [14,18].

In order to lessen the adverse reactions of general anesthesia based on opioids in patients undergoing total laparoscopic hysterectomy and improve their postoperative recovery quality, esketamine-based opioid-sparing anesthesia strategy was selected in this study. By comparing the traditional general anesthesia strategy, the indexes such as postoperative pain score and recovery quality were observed, so as to provide research evidence for the opioid-sparing anesthesia strategy.

2. Methods and materials

2.1. Study design and ethics

This is an assessor-blinded parallel-group randomized controlled trial and has been approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (KJX-2021-030-01) on May 20, 2021. The research project was formally recorded in the Chinese Clinical Trial Registry with the registration number ChiCTR2100051465 on the September 24, 2021. All participants submitted written consent prior to participation. The trial report adheres to the guidelines set forth by the Consolidated Standards of Reporting Trials (CONSORT) checklist.

2.2. Participants

For every patient, written informed permission was acquired. The criteria for inclusion were female patients aged 18 to 65, with a BMI ranging from 18 to 25 kg/m2. American Society of Anesthesiologists (ASA) physical status I-II, and an inpatient elective complete laparoscopic hysterectomy scheduled. The following were the exclusion standards: esketamine allergy; alcohol addiction; nervous system disorders; and chronic use of sedatives or hypnotics; moderate to severe hypertension and (or) patients for whom a notable increase in blood pressure would pose a severe risk; significant malfunction of the kidneys and liver; serious malfunction of the heart and lungs; refusal to sign informed consent, and uncooperative or legally incapable. If the surgical procedure was altered or the patient retained endotracheal tubes after surgery, they were also excluded from being able to participate in the trial.

2.3. Randomization and blinding

Every participant included in the study was assigned in a random manner to either the trial group, denoted as group K, or the control group, referred to as group C, in an equal proportion of 1:1. A research nurse created a block randomization plan with fixed block size and stratified block randomization using an online random number generator (www.random.org). Only researchers are allowed to open the opaque sealed envelope containing each patient's anesthetic method information before the start of anesthesia. The group allocation was concealed from all patients, surgeons, follow-up evaluators post-surgery, and doctors who performed statistical analysis. There was no way to blind the anesthesiologist administering general anesthesia because of the groups' varied drug administration methods. They did not, however, take part in postoperative data collection or assessment of postoperative outcomes.

2.4. Anesthesia methods

Prior to beginning the trial, the patients received instructions regarding the utilization of a Visual Analog Scale (VAS) for pain assessment. (VAS score: 0–10 cm, indicating painless to most painful) The Visual Analogue Scale (VAS) classifies mild pain by assigning a score ranging from 0 to 3, while moderate pain is categorized with scores between 4 and 7, and severe pain corresponds to scores between 8 and 10. In cases where the VAS score in the PACU exceeded 4, individuals were promptly instructed to obtain analgesia in order to increase adherence to the procedure. All patients received dexamethasone 8 mg for PONV prophylaxis.

Prior to surgery, every individual fasted for 8 h and avoided water for 4 h. Anesthesia was administered by an anesthesiologist in accordance with the following standardized procedure. Upon entering the operating room, participants' heart rate (HR), pulse oxygen saturation (SpO2), and upper-limb mean blood pressure (MBP) were observed together with the characteristics of the electrocardiogram (ECG), and baseline values were established. A crystalloid solution was started once an intravenous line was inserted. Preoxygenation was given to all patients.

For group C, anesthesia was induced by administering intravenous injections of midazolam at a dosage of 0.05 mg/kg, propofol at a dosage range of 1.5–2 mg/kg, and sufentanil at a dosage of 0.50 μg/kg. Once the loss of consciousness (LOC) was confirmed, an injection of 0.60 mg/kg of rocuronium was administered. LOC is defined as loss of verbal responsiveness and eyelash reaction. After zero TOF (Muscle relaxation monitor, Veryark, Nanning, Guangxi) twitches were achieved, using a video laryngoscope, an endotracheal tube with an inner diameter of 7 mm was placed in the patient's trachea. Anesthesia maintenance was achieved using propofol at a rate of 4–6 mg/kg/h and remifentanil at a rate of 0.15–0.3 μg/kg/min, subsequent to anesthesia induction. In group K, anesthesia was initiated through the intravenous administration of midazolam 0.05 mg/kg, propofol 1.5–2 mg/kg, sufentanil 0.30 μg/kg, esketamine 0.30 mg/kg and rocuronium 0.6 mg/kg, and maintained with 4–6 mg/kg/h propofol, 0.06–0.10 μg/kg/min remifentanil, and 0.125 mg/kg/h esketamine after intubation. During the surgical procedure, the pumping rate of remifentanil and propofol was manipulated to titrate the two groups' bispectral index (BIS) values between 40 and 60, which is the acceptable range (BIS A-2000BIS, Aspect Medical Systems, Inc. Norwood, MA 02062 USA)

Respiratory rate of 10–15 times per minute, tidal volume of 6–8 mL per kilogram, and oxygen intake flow of 2 L per minute were all established. Throughout the entire process, mechanical ventilation was utilized to regulate the concentration of carbon dioxide at the end of expiration as needed, ensuring it remained within the range of 35–45 mmHg. Additional rocuronium was administered as needed. The intra-abdominal pressure varied between 9 and 13 mmHg when pneumoperitoneum was established. Throughout the procedure, the variation in the patient's blood pressure does not surpass 20 % of the original value. If the mean blood pressure (MBP) was less than 30 % of the baseline value and the heart rate was less than 50 beats, it was recommended to give 3–6 mg ephedrine and 40ug phenylephrine when the heart rate was more than 50 beats. If the MBP was greater than 30 % of the baseline, 5 mg urapidil was given, and if the HR was less than 40 times/minute, 0.5 mg atropine was injected. If necessary, these procedures were repeated.

The infusions of esketamine, propofol, and remifentanil were terminated at the start and finish of the skin suturing process, respectively. Taking into account the distinct pharmacokinetics of the medications employed in every study arm, the patients were relocated to the post-anesthesia care unit (PACU) in order to recover and remove the endotracheal tube. The individual's respiratory and hemodynamic indicators are also recorded in the PACU. The anesthesiologist in the PACU was unaware of the grouping situation. A patient was given 30 mg of ketorolac tromethamine if their VAS score in the PACU was exceeding four points, indicating inadequate analgesia. Respiratory depression was considered when the patient's SpO2 was less than 90 % or their breathing frequency was fewer than 6 breaths per minute. One investigator who was blind to the patients' study group questioned patients on the existence of nausea, vomiting, pruritus, headache, dizziness, and visual abnormalities during the designated measurement times, namely PACU, 6, 24, and 48 h. Ramsay sedation scale was used to measure the sedation level of patients in recovery room and ward following surgery.

2.5. Outcome measures

The main results of this research were QoR-40 on the first postoperative day and pain in the PACU and ward, including the highest VAS pain levels within the six, twenty-four, and 48 h following surgery.

The secondary outcome indicators for this study included the total amount of sufentanil, remifentanil, and propofol used during the procedure, as well as hemodynamic data such as the profile of MAP, HR, and SpO2 at various measurement times (T0: before induction, T1: after induction, T2: immediately after tracheal intubation, T3: after artificial pneumoperitoneum, T4: at cessation of anesthetics, T5: immediately after extubation). Additionally, postoperative opioid-related adverse events were recorded.

2.6. Data collection

The study recorded the age, body mass index (BMI), ASA physical status class, duration of surgery and anesthesia, intraoperative sufentanil, remifentanil, and propofol consumption, time to recovery of consciousness (ROC), time to recovery of spontaneous breathing, and time to extubation for each patient.

2.7. Statistical analysis

The primary metric used to assess the results of the study was the global Quality of Recovery-40 (QoR-40) score on the initial day following the surgical procedure. We conducted calculations to determine the sample size using the premise that a variation of at least 10 points in the QoR-40 score is clinically significant. Taking into account that a difference of 10 points translates into a 15 %

advancement in the quality of the recuperation, the calculations for sample size indicated that 34 individuals per group were necessary to ensure a statistical power of 90 % while maintaining a type 1 error rate of 0.05. We enrolled a minimum of 80 participants to accommodate a 20 % drop-out rate. Statistical analysis was performed on the demographic and perioperative data, as well as the primary and secondary outcomes, for each study group. Utilizing the Kolmogorov-Smirnov test, the normality of the quantitative variable distribution was examined. Utilizing either the Mann-Whitney *U* test or the independent-sample *t*-test, the quantitative variables were analyzed along with the primary outcome (QoR-40). Nominal variables were summarized as frequency (percentage-%) and continuous variables as mean ± standard deviation (SD) or median (inter quartile range -IQR). Absolute Standardized Differences (ASD) were calculated to assess the balance among the two groups regarding baseline characteristics of patients, with the assumption that the critical value of imbalance was 0.20. A statistical significance level of $P < 0.05$ was considered significant. We calculated the sample size with PASS 15.0 software. Statistical analyses were carried out using the SPSS 25.0 software package. The software used to create the graphs was GraphPad Prism version 4.00 for Windows.

3. Results

Ninety-four patients underwent eligibility evaluation; two were excluded for not meeting the inclusion criteria, and the remaining two declined to participate. As a result, we analyzed the data from 90 patients, 45 of them were in group C and 45 were in group K, respectively (Fig. 1).

No discernible variations were observed in the baseline characteristics of the two groups (Table 1). By surgical procedure, there were no notable distinctions observed in estimated amount of blood loss, the duration of the surgical procedure and anesthesia, as well as the time in which pneumoperitoneum was maintained ($P>0.05$).

The primary outcomes of this study are summarized in Table 2. Group K had substantially superior mean (SD) global QoR-40 score after the operation compared to group C (Table 2). Accordingly, significant differences exist in Visual Analogue Scale (VAS) scores for periods of rest and activity between the two groups, regardless of whether it is in the PACU or ward. Nevertheless, the Ramsay scores exhibited no variation between the groups (Table 2). On the first postoperative day, group K's QoR-40 scores were higher than group

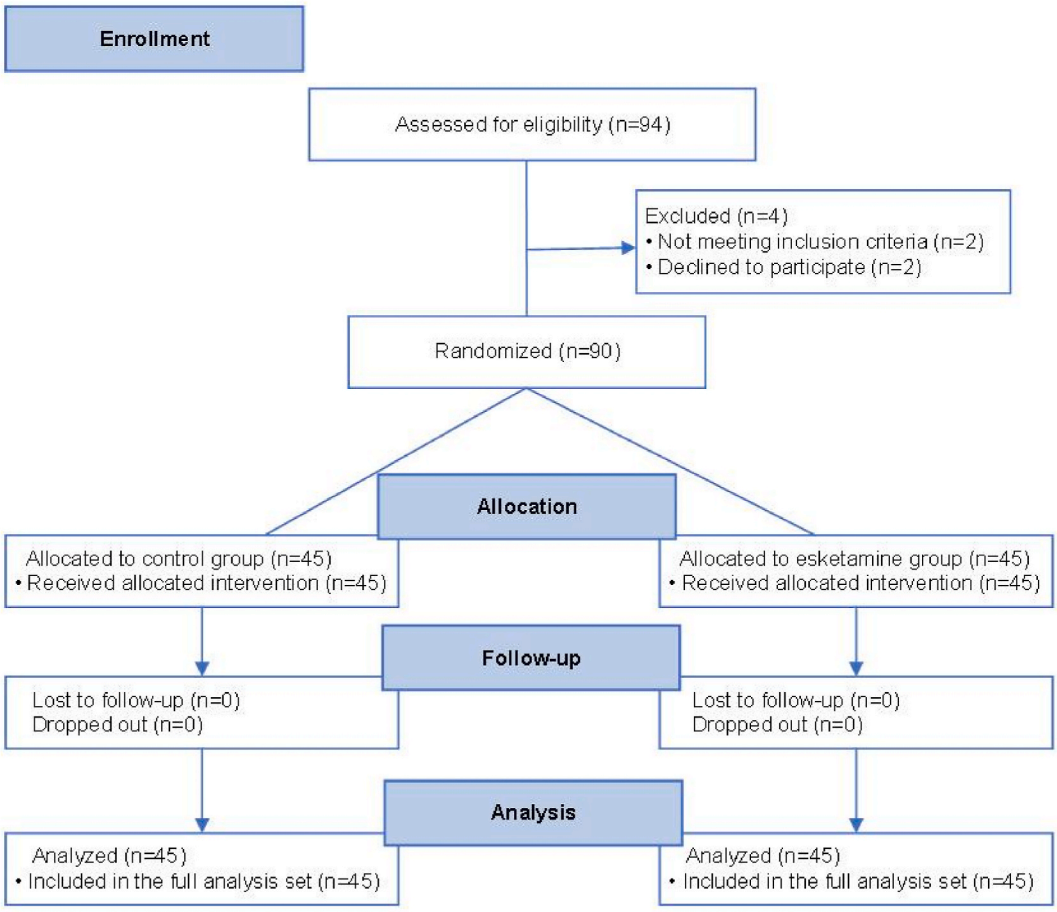

Fig. 1. CONSORT diagram describing patient progress through each stage of the randomized trial.

Table 1
Baseline patient characteristics and surgical and anesthetic data.

	Group C (n = 45)	Group K (n = 45)	ASD	*P*-value
Age (y)	47.33 ± 11.10	43.22 ± 9.31	0.02	0.959
BMI (kg/m$^{2)}$	22.98 ± 1.95	23.39 ± 1.80	0.21	0.302
ASA physical status, n (%)			0.08	>0.999
I	4 (8.9)	3 (6.7)		
II	41 (91.1)	42 (93.3)		
Smoking status, n (%)			0.05	0.851
Nonsmoker	42 (93.3)	42 (93.3)		
Former smoker	2 (4.4)	1 (2.2)		
Current smoker	1 (2.2)	2 (4.4)		
History of PONV or motion sickness, n (%)	2 (2.2)	3 (6.7)	0.08	>0.999
History of abdominal surgery, n (%)	4 (8.9)	2 (4.4)	0.15	0.673
Preoperative QoR-40 score	181.44 ± 6.95	180.56 ± 5.96	0.14	0.516
Duration of anesthesia (min)	105.89 ± 16.35	103.96 ± 27.51	0.08	0.686
Duration of surgery (min)	90.67 ± 14.60	88.22 ± 25.27	0.11	0.576
Duration of pneumoperitoneum (min)	76.44 ± 17.67	73.11 ± 22.67	0.16	0.436
Estimated blood loss (ml)	78.22 ± 23.86	70.89 ± 20.76	0.33	0.123

Data are presented as the mean ± SD, median [interquartile range], or number of patients (%).
ASA: American Society of Anesthesiologists; ASD: Absolute standardized difference anesthesia; BMI: Body Mass Index.

Table 2
Primary outcomes.

	Group C (n = 45)	Group K (n = 45)	Mean Difference (95 % CI)	*P*-value
QoR −40 on postoperative Day 1				
Total	151.47 ± 8.35[a]	160.91 ± 9.12[a]	−9.44 (-13.11, −5.78)	<0.001
Physical comfort	41.60 ± 4.20[a]	48.26 ± 5.93[a]	−6.67 (-8.82, −4.51)	<0.001
Emotional state	36.42 ± 3.35[a]	38.11 ± 1.94[a]	−1.69 (-2.84, −0.54)	0.005
Physical independence	16.73 ± 1.19[a]	16.82 ± 1.39[a]	−0.89 (-0.63,0.45)	0.745
Psychological support	29.35 ± 1.26[a]	29.31 ± 1.36[a]	0.04 (-0.51,0.60)	0.837
Pain	27.35 ± 1.91[a]	28.40 ± 1.39[a]	−1.04 (-1.74, −0.35)	0.004
Postoperative pain scores at rest				
PACU	3.07 ± 0.86[a]	2.38 ± 0.68[a]	0.69 (0.36,1.01)	<0.001[c]
	3 (2–3) [2–5][b]	2 (2–3) [2–5][b]		<0.001[d]
At 6 h	3.35 ± 0.93[a]	3.00 ± 0.73[a]	0.36 (0.00,0.70)	0.048[c]
	3 (3–4) [2–6][b]	3 (3-3) [2–5][b]		0.047[d]
At 24 h	2.82 ± 0.18[a]	2.27 ± 0.58[a]	0.56 (0.28,0.82)	<0.001[c]
	3 (2–3) [1–4][b]	2 (2–3) [1–4][b]		<0.001[d]
At 48 h	1.68 ± 0.51[a]	1.42 ± 0.50[a]	0.26 (0.05,0.48)	0.014[c]
	2 (1–2) [1–3]]b	1 (1–2) [1,2][b]		0.017[d]
Postoperative pain scores on movement rowhead				
PACU	5.69 ± 0.82[a]	4.91 ± 0.76[a]	0.78 (0.45,1.11)	<0.001[c]
	6 (5–6) [4–7][b]	5 (4–5) [4–7][b]		<0.001[d]
At 6 h	6.04 ± 0.77[a]	5.49 ± 0.69[a]	0.56 (0.25,0.86)	0.001[c]
	6 (5–7) [5–8][b]	5 (5–6) [4–7][b]		0.001[d]
At 24 h	4.11 ± 0.93[a]	3.85 ± 0.76[a]	0.26 (-0.09,0.61)	0.006[c]
	4 (3–5) [3–7][b]	4 (3–4) [2–6][b]		0.242[d]
At 48 h	1.80 ± 0.50[a]	1.86 ± 0.34[a]	−0.07 (-0.24,0.11)	0.466[c]
	2 (1.5–2) [1–3][b]	2 (2-2) [1,2][b]		0.403[d]
Postoperative sedation scores				
PACU	2.84 ± 0.82[a]	2.91 ± 0.63[a]	−0.07 (-0.37,0.24)	0.668[c]
	3 (3-3) [1–5][b]	3 (3-3) [1–5][b]		0.875[d]
At 6 h	2.73 ± 0.98[a]	2.89 ± 0.68[a]	−0.16 (-0.51,0.20)	0.386[c]
	3 (2–3) [1–5][b]	3 (3-3) [1–5][b]		0.448[d]
At 24 h	1.96 ± 0.48[a]	2.18 ± 0.44[a]	−0.11 (-0.27,0.05)	0.024[c]
	2 (1–2) [1–3][b]	2 (2-2) [1–3][b]		0.026[d]
At 48 h	1.96 ± 0.21[a]	1.98 ± 0.15[a]	−0.02 (-0.10,0.05)	0.562[c]
	2 (2-2) [1,2][b]	2 (2-2) [1,2][b]		0.559[d]

Abbreviations: CI, confidence interval; QoR-40, 40-item quality of recovery questionnaire.
Pain scores: VAS 0–10 cm; sedation scores: Ramsay 1-6.
Note:48h: the second 24h (24h–48h).
[a] mean ± standard deviation; [b] median (25th – 75th percentiles) [minimum – maximum] of raw data.

C's (160.91 ± 9.11 vs 151.47 ± 8.35, respectively; mean difference 9.44 [95 % confidence interval: 5.78–13.11]; $P < 0.001$). Group K demonstrated notably higher scores for postoperative physical comfort, emotional state, and pain dimensions compared to group C (mean difference:6.67, 95 % CI [4.51–8.82], and $P < 0.001$; 1.69, 95 % CI [0.54–2.84], and $P < 0.01$; 1.04, 95 % CI [0.35–1.74], and *P*

< 0.01). No notable disparity was detected in the remaining dimensions of QoR-40 when comparing the two groups (Table 2).

In the initial 48 h following the operation, the VAS scores of group K exhibited significant differences from those of group C, as demonstrated in Table 2. Especially, significant differences in terms of resting pain were detected within 48h postoperatively between the two groups ($P < 0.05$ for each). In the comparison between group C and group K, the VAS scores on movement were remarkably higher in group C within 24 h after surgery. However, Table 2 demonstrates that in the second 24 h following the procedure, there existed no statistically significant discrepancy in the pain scores on movement when comparing the two groups (1.80 ± 0.50 vs 1.86 ± 0.34, $P > 0.05$). There was a noticeable decrease in pain severity experienced over the research period after 6h of operation. Sedative scores did not differ markedly between group C and group K throughout the trial ($P>0.05$ for each) (Table 2).

There were no observed variations in relation to the incidence of nystagmus, hallucination, pruritus, dizziness, shivering, headache in the PACU and within 6, 24, and 48h in the ward post-operatively between the two groups. Within 6 h following surgery, group C experienced a considerably higher incidence of fever, nausea, and vomiting than the trial group (14 (31,1 %) vs 5 (11.1 %), $P < 0.05$; 15 (33.3 %) vs 6 (13.3 %) $P < 0.05$; 10 (22.2 %) vs 2 (4.4 %) $P < 0.05$). The incidence of vomiting was statistically significant between the two groups within 24h (17 (37.8 %) vs 5 (11.1 %), $P < 0.01$). There were no significant differences in terms of nausea and vomiting between 24h and 48h in the ward (6 (13.3 %) vs 2 (4.4 %), $P > 0.05$; 3 (6.7 %) vs 1 (2.2 %), $P > 0.05$) (Table 3).

Table 4 shows the Intraoperative data, PACU date as well as postoperative data. There were no substantial disparities observed between the two groups in terms of ROC, spontaneous respiratory recovery, directional recovery and extubation time. The total dose of sufentanil, remifentanil and propofol (Fig. 2 (A, B, C)), the number of patients in the ward in need of rescue antiemetics and the total duration of the postoperative hospital stay were both shorter in the group K than the control group (17.28 ± 2.59 vs 43.43 ± 3.52, $P < 0.001$; 0.51 ± 0.15 vs 1.24 ± 0.24, $P < 0.001$; 592.67 ± 92.28 vs 761.11 ± 114.04, $P < 0.001$; 2 (4.4 %) vs 10 (22.2 %), $P < 0.05$; 5 [5–8] vs 6 [5–8], $P < 0.05$) (Table 4).

The perioperative hemodynamic variables, such as SpO_2, MAP, and HR, were displayed in Fig. 2. Changes in HR and MAP were different between the groups at T1 and T2 ($P < 0.05$ Fig. 2). Post-hoc analysis revealed a statistically noteworthy rise in HR in group K as opposed to group C at T1 and T2 after induction (Fig. 2 (D)). MAP increased considerably in group K following induction ($P < 0.05$) and right after tracheal intubation ($P < 0.01$ Fig. 2 (E)). There was an absence of distinguishable disparity in SpO2 levels observed between group K and group C ($P > 0.05$ Fig. 2 (F)). Table 4 displayed a comparison of hypotensive occurrences between the groups. Group C had a higher percentage of patients who utilized ephedrine during surgery than Group K (10 (22.2 %) vs 2 (4.4 %), $P < 0.05$).

4. Discussion

In contrast to patients receiving opioid-based anesthesia using remifentanil, the current study showed that patients receiving

Table 3
Cumulative incidence of postoperative adverse events.

	Group C (n = 45)	Group K (n = 45)	*p*-value
	PACU data		
Nausea, n (%)	13 (28.9)	4 (8.9)	0.031
Vomiting, n (%)	5 (11.1)	1 (2.2)	0.205
Respiratory depression, n (%)	7 (15.6)	2 (4.4)	0.026
Nystagmus, n (%)	0 (0)	0 (0)	>0.999
Hallucination, n (%)	0 (0)	0 (0)	>0.999
	GW data (6h)		
Nausea, n (%)	15 (33.3)	6 (13.3)	0.025
Vomiting, n (%)	10 (22.2)	2 (4.4)	0.030
Respiratory depression，n (%)	2 (4.4)	0 (0)	0.153
Fever，n (%)	14 (31.1)	5 (11.1)	0.039
	GW data (24h)		
Nausea, n (%)	19 (42.2)	10 (22.2)	0.042
Vomiting, n (%)	17 (37.8)	5 (11.1)	0.007
Pruritus, n (%)	0 (0)	0 (0)	>0.999
Headache, n (%)	7 (16.6)	5 (11.1)	0.535
Dizziness, n (%)	15 (33.3)	9 (20)	0.153
Shivering, n (%)	0	0	>0.999
Fever，n (%)	13 (27.1)	5 (11.1)	0.092
	GW data (48h)		
Nausea, n (%)	6 (13.3)	2 (4.4)	0.138
Vomiting, n (%)	3 (6.7)	1 (2.2)	0.306
Pruritus, n (%)	0 (0)	0 (0)	>0.999
Headache, n (%)	3 (6.7)	1 (2.2)	0.306
Dizziness, n (%)	8 (17.8)	5 (11.1)	0.368
Shivering, n (%)	0	0	>0.999
Fever，n (%)	7 (15.2)	2 (4.4)	0.171

Data are presented as the median [interquartile range] or number of patients (%).
ROC: recovery of consciousness; CI: confidence interval; PACU: post-anesthesia care unit; GW: general ward.
Note:48h: the second 24h (24h–48h).

Table 4
Perioperative data between the two groups.

	Group C (n = 45)	Group K (n = 45)	Mean difference (95 % CI)	*P*-value
Intraoperative data				
Consumption of sufentanil (ug)	43.43 ± 3.52	17.28 ± 2.59	26.15 (24.86,27.44)	<0.001
Consumption of remifentanil (mg)	1.24 ± 0.24	0.51 ± 0.15	0.73 (0.65,0.81)	<0.001
Consumption of propofol (mg)	761.11 ± 114.04	592.67 ± 92.28	168.44 (124.98,211.93)	<0.001
Use of vasoactive drugs				
Ephedrine, n (%)	10 (22.2)	2 (4.4)	/	0.030
Noradrenaline, n (%)	1 (2.2)	0 (0)	/	>0.999
Urapidil, n (%)	1 (2.2)	3 (6.7)	/	0.609
Atropine, n (%)	3 (6.7)	3 (6.7)	/	>0.999
PACU data				
Time to ROC (min)	9.87 ± 2.75	10.97 ± 3.40	−1.11 (-2.40,0.18)	0.092
Time to recovery of self-respiration (min)	7.58 ± 2.18	7.68 ± 2.94	−1.11 (-1.20,0.97)	0.839
Time to extubation (min)	14.67 ± 3.85	15.86 ± 3.33	−1.20 (-2.7,0.30)	0.117
Time to orientation recovery (min)	18.56 ± 4.06	18.87 ± 3.55	−3.11 (-1.9,1.28)	0.700
Need of rescue analgesics, n (%)	4 (8.9)	1 (2.2)	/	0.375
Need for rescue antiemetics, n (%)	3 (6.7)	0 (0)	/	0.240
GW data				
Need of rescue analgesics, n (%)	7 (15.6)	2 (4.4)	/	0.160
Need for rescue antiemetics, n (%)	10 (22.2)	2 (4.4)	/	0.030
Time to first exhaust (h)	26.04 ± 4.24	25.77 ± 4.58	0.26 (-1.58,2.11)	0.266
Duration of postoperative hospital stay (day)	6 [5–8]	5 [5–8]	1 (1,1)	0.048

Data are presented as the median [interquartile range] or number of patients (%).
ROC: recovery of consciousness; CI: confidence interval.

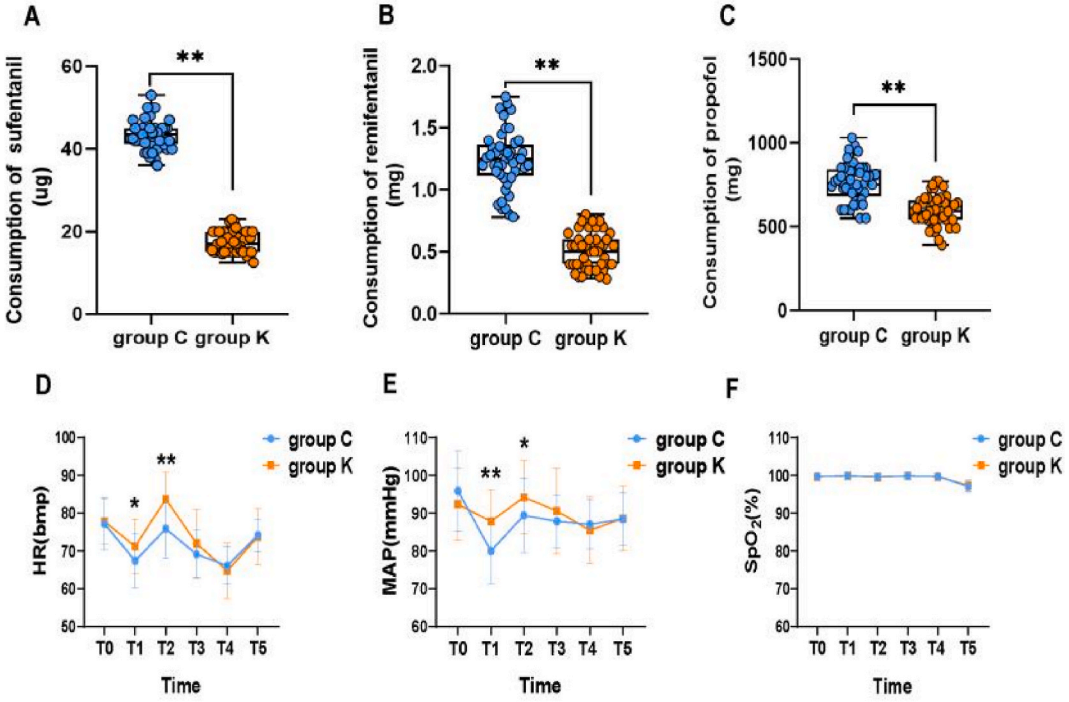

Fig. 2. Consumption of sufentanil (A), remifentanil (B) and propofol (C) and hemodynamic outcomes. Perioperative hemodynamic variables including (D) HR, (E) MAP, (F) SpO_2. T0: before induction; T1: after induction; T2: immediately after tracheal intubation; T3: after artificial pneumoperitoneum; T4: at cessation of anesthetics; T5:immediately after extubation.posthoc analysis. HR: heart rate; MAP: mean arterial pressure; SpO2: pulse oxygen saturation Group C = control group; group K = esketamine group. *Compared with Group C, P < 0.05, **Compared with Group C, P < 0.01.

opioid-sparing anesthesia based on esketamine possess superior recuperative quality. Furthermore, the total score of the QoR-40 scale, along with the scores attributed to its dimensions of physical comfort, emotional state, and pain, exhibited a discernible elevation compared to those recorded for the group C. Additionally, the Visual Analog Scale (VAS) scores during both periods of rest and movement post-surgery demonstrated marked superiority in comparison to the corresponding scores of the group C. Group K had

better hemodynamic maintenance, less intraoperative hypotension, and fewer postoperative adverse events.

The quality of recovery measured by the QoR-40 questionnaire was the primary outcome of the study. The QoR-40 questionnaire incorporates five health dimensions: physical comfort, emotional state, physical independence, psychological support, and pain. Prior research has proved that QoR-40 provides a thorough evaluation of the patient's postoperative recovery quality, focusing on patient-centered outcomes [19–21]. Based on previous research, an elevation of 10 points is correlated with a 15 % [22] enhancement in recovery quality. Moreover, a minimum clinical relevant discrepancy of 6.3 points has been determined for QoR-40 score [23]. Stated differently, the alteration that occurred due to the perioperative intervention may be seen as an indication of a substantial shift in health condition. The current study indicated that the administration of perioperative intravenous low-dose esketamine and opioids led to a notable augmentation of 9.4 points compared with group C in QoR-40 scores on the first day following surgery. Additionally, the disparity observed between the groups surpassed the threshold considered as the minimal clinically significant difference. A study of Video-Assisted Thoracic Surgery [24] found that patients under esketamine-based anesthesia obtained higher QoR-40 than patients under anesthesia based on opioids, as indicated in our study. In contrast, according to one study [25], the administration of ketamine did not result in an enhancement of the recovery outcome for patients subsequent to laparoscopic cholecystectomy, as measured through the utilization of the QoR-40 survey. The discrepancy was possibly attributed to dissimilarities in the dosage and manner in which ketamine was administered, along with the variances in surgical traumas encountered by our patient.

One of the primary concerns with total laparoscopic hysterectomy is insufficient postoperative pain relief. Previous research revealed that intravenous ketamine administered during the perioperative phase lowered pain levels both at rest and during periods of movement [26,27]. Likewise, the present study revealed that the group administered with esketamine exhibited reduced pain scores as assessed using the VAS in both the PACU and the ward, within a 48-h timeframe following the surgical procedure. The disparities in mean pain scores displayed statistically noteworthy results in the initial 24 h following the surgical procedure, regardless of the patient being at rest or engaged in movement. It is worth noting that the elimination half-life of esketamine is 2–3 h. Previous research reported a significant effect of ketamine on immediate, but not late postoperative pain after surgery [28]. However, in this trial, we observed that the esketamine group had lower pain scores within 48h of surgery. Various studies have indicated that the combination of ketamine and remifentanil can effectively prevent opioid-induced hyperalgesia in major abdominal surgeries, thereby enhancing postoperative analgesia and extending the duration thereof. Numerous scholars have attested that the involvement of NMDA receptors is associated with the mechanisms underlying opioid-induced hyperalgesia (OIH), and that the application of NMDA receptor antagonists can minimize its occurrence [29]. It has been documented that short-acting opioids, such remifentanil, cause the overproduction of reactive oxygen species and proinflammatory cytokines, activating neuronal NMDA receptors in the process. These events are critical to the development of OIH [30]. Therefore, the author speculated that the lower VAS scores in group K within 48 h could be related to the inhibition of OIH by esketamine. Moreover, numerous earlier studies found that esketamine effectively reduced the percentage of individuals experiencing moderate to severe pain when resting. This reduction corresponded to the discrepancy observed in the pain dimension score as assessed by the QoR-40 [31].

Aside from pain, the notable differences between groups K and C are physical comfort and emotional state. PONV (post-operative nausea and vomiting) has been associated with poorer quality of recovery [32]. Given that female patients having gynecological laparoscopy are at risk for PONV, it was anticipated that a high incidence of PONV would be present in the patients who took part in our study [33]. Ketamine was found to attenuate PONV in one study [17]. In contrast to that review, other research[32] did not identify a link between ketamine and decreased PONV. In our study, less nausea and vomiting were observed in patients who were administered opioid-sparing anesthesia utilizing esketamine, in contrast to group C.

Because of the decrease in perioperative opioid intake, opioid-sparing anesthesia based on esketamine may have helped to reduce the incidence of PONV. Physical comfort may have improved as a result of less nausea and vomiting. Aside from the effect of PONV on physical comfort, the different anesthetic method may affect the modulation of the stress response, which is one of the reasons why physical comfort was higher in group K in our study. The implementation of anesthesia and the occurrence of surgical trauma can potentially elicit immunological and inflammatory reactions. Several studies have demonstrated that ketamine possesses not only anesthetic properties, but also anti-inflammatory properties. These properties have been observed in numerous studies, including preclinical and clinical trials conducted both in vitro and in vivo [34,35]. The anti-inflammatory effects of ketamine have been demonstrated when the medication was provided prior to and after immune activation, indicating that ketamine may be able to prevent worsening of inflammation as well as lessen existing inflammation [36]. In our research, it was noted that the incidence of fever in group K was comparatively less pronounced than in the control group, particularly after 6 h following the operation.

Emotional state is a component of the QoR-40 questionnaire that assesses the emotional well-being and state of patients after surgery. It aims to capture the patient's overall emotional experience during recovery. Patients were asked to rate statements related to their emotions, such as feeling irritable, depressed, anxious, lonely or unable to sleep, their ability to control their emotions and their overall emotional status. Esketamine has demonstrated its efficacy in multiple clinical contexts by diminishing clinical manifestations associated with depression. Recently, the European Union has granted authorisation for the expanded utilization of esketamine to facilitate the rapid reduction of symptoms associated with depression [37,38]. The previous study [39] indicated that the perioperative administration of esketamine proved to be efficacious in mitigating the occurrence of postoperative depression among individuals receiving breast cancer surgery. Similarly, group K had improved emotional states and was less likely to experience depression, irritability, or sleep difficulties when contrasted with patients belonging to group C. Clinicians who followed up after surgery realized that esketamine might be helpful in relieving post-operative depression and poor mood. This could be linked to the general improvement in pain and physical comfort, suggesting that the use of esketamine considerably enhanced both physical and psychological postoperative quality of life. No noteworthy disparity was detected in the scores pertaining to psychological support when comparing the two groups.

A clinical trial [40] indicated that the perioperative application of esketamine may result in a reduction of propofol dosage by approximately 20 %. Furthermore, no discernible difference was seen in the occurrence of negative medication reactions when comparing both groups. There was an absence of statistical disparity observed in the occurrence of adverse effects related to ketamine, as there had been in prior trials of intraoperative ketamine. In our research, the author did not discern any detrimental consequences associated with ketamine, and the dosage of propofol was also reduced. Furthermore, the incidence of hypotension caused by anesthesia with ketamine is relatively low, which is consistent with the study results [40]. Post-induced hypotension, which is frequently seen during the induction of opioid-based anesthesia, raises the danger of myocardial injury (decrease of myocardial blood perfusion and oxygen supply). Compared with the blood pressure of group K, the blood pressure of group C after induction and before intubation decreased significantly, and the percentage of vasopressors used in group C was higher, indicating a statistical difference. Upon comparison with the baseline level, it was observed that patients' HR and MAP decreased following anesthetic induction. The heart rate and average arterial pressure observed in group K following the administration of anesthesia induction were found to be higher in comparison to those observed in group C. Esketamine produced an indirect stimulation of the cardiovascular system through its activation of the sympathetic nervous system, thereby assisting in the maintenance of stable hemodynamics. The comprehensive manifestations are increased HR and blood pressure. After the tracheal intubation procedure, group K had a temporary increase in heart rate compared to group C. We engaged in speculation due to the possibility that the commencement time of ketamine could be marginally delayed compared to that of conventional intravenous induction medications.

Depending on the trial protocol, different rescue procedures and drugs were to be implemented in the event that tachycardia or persistently elevated blood pressure occurred. Statistical analysis revealed no significant disparity between the two groups. Despite the authors' observation of an improved quality of recovery in group K, the advantages did not result in a decreased duration of hospitalization post-operation. Compared to group C, group K's hospital stay following surgery (measured in days) was longer, (6 [5–8] vs 5 [5–8], $P = 0.048$), but the number of samples in this study is slightly smaller than needed to define a length of stay difference in outcomes.

There may be some limitations of this study. For starters, we did not use any other medications in our study of esketamine's opioid-sparing impact beyond those listed above. Second, all of the patients in this study were adult females in generally good health. Individuals with significant co-occurring illnesses or chronic pain were excluded. Hence, additional verification is required to prove the generalizability of the study findings. Furthermore, the predicted sample size, as determined by the overall score of QoR-40, might not suffice in order to discern disparities in the five dimensions of QoR-40 among the two groups.

5. Conclusions

In conclusion, this study demonstrated that the esketamine-based opioid-sparing anesthesia strategy can effectively improve the quality of recovery as well as alleviate postoperative pain in patients having total laparoscopic hysterectomy, particularly in the early stages of the postoperative period. Subsequent clinical trials ought to concentrate on identifying the surgical patients who will most profit from opioid-sparing with better efficacy and lower cost.

Additional information

No additional information is available for this paper.

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Ethics approval and informed consent

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (KJX-2021-030-01) on May 20, 2021, and it was completed in accordance with the Declaration of Helsinki's guiding principles. Obtainsion of written informed consent was gained from every participant of the trial, and the study was duly registered with the China Clinical Trials Registry (ChiCTR2100051465; September 24, 2021).

Consent for publication

Not applicable.

Data availability statement

The data employed in the present study may be obtained from the corresponding author upon making a reasonable request. The data cannot be accessed publicly because the subsequent phase of the research is still ongoing.

CRediT authorship contribution statement

Jialei Liu: Writing – original draft. **Jiangwen Yin:** Writing – original draft. **Jieting Yin:** Data curation. **Menghan Zhou:** Data curation. **Long Chen:** Data curation. **Xiwei Dong:** Writing – review & editing, Project administration. **Yan Li:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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