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CLINICAL TRIAL REPORT

Comparison of Postoperative Analgesic Efficacy of Oliceridine and Sufentanil in Total Laparoscopy Hysterectomy, a Clinical Double-Blind Controlled Trial

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Objective: To compare the postoperative analgesic efficacy of oliceridine versus sufentanil in patients undergoing total laparoscopy hysterectomy.

Methods: In this double-blind, randomized controlled trial, 80 patients scheduled for elective total laparoscopy hysterectomy were allocated in a 1:1 ratio to receive postoperative patient-controlled intravenous analgesia (PCIA) with either oliceridine (Group O) or sufentanil (Group S). The primary outcome was the cough Numeric Rating Scale (NRS) score at 6 hours postoperatively. Secondary outcomes included resting and cough NRS scores at 0.5, 2, 6, 12, 24, and 48 hours (excluding the 6-hour cough NRS), number of PCIA attempts, proportion requiring rescue analgesia, total rescue analgesic dose, time to first flatus and ambulation, and 24-hour postoperative recovery quality assessed by the 15-item Quality of Recovery (QoR-15) scale. Exploratory outcomes included hemodynamic parameters within 30 minutes after the analgesic loading dose, anesthesia emergence time, and tracheal extubation time. Safety outcomes comprised the incidence of adverse events within 48 hours postoperatively.

Results: No significant differences were found between groups in resting or cough NRS scores at any time point, PCIA attempts, rescue analgesia requirement, rescue tramadol dose, emergence time, or extubation time. However, Group O had a significantly shorter time to first flatus (18.63 ± 3.51 vs 24.70 ± 3.26 hours, $P < 0.001$) and time to first ambulation (17.95 ± 3.30 vs 20.28 ± 3.76 hours, $P = 0.004$), a lower overall incidence of adverse events (32.5% vs 62.5%, $P = 0.007$), and a higher QoR-15 score (120.85 ± 7.15 vs.115.63 ± 6.74, $P = 0.001$). Additionally, Group O demonstrated better hemodynamic stability than Group S.

Conclusion: For patients undergoing total laparoscopy hysterectomy, oliceridine provides postoperative analgesic efficacy comparable to sufentanil but is associated with a lower incidence of adverse events and better recovery quality.

Keywords: oliceridine, sufentanil, postoperative analgesia, adverse events

Introduction

Effective postoperative analgesia is essential for promoting recovery, reducing discomfort, and encouraging early movement after surgery.[1] Opioids remain the cornerstone of perioperative pain management due to their potent analgesic properties.[2] Commonly used agents such as sufentanil are widely employed for both intraoperative anesthesia and postoperative pain management. However, their clinical utility is significantly limited by dose-dependent adverse events,

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including respiratory depression, sedation, nausea, vomiting, pruritus, and reduced gastrointestinal motility.[3] Opioid-induced respiratory depression, in particular, may lead to severe hypoxia and respiratory distress.[4] A 2018 retrospective study indicated that over 10% of adult patients receiving opioids after surgical or endoscopic procedures experienced at least one opioid-related adverse events (ORAEs).[5]

Traditional opioids exert their pharmacological effects primarily through non-selective activation of the μ-opioid receptor, engaging both G-protein and β-arrestin signaling pathways.[6] Analgesia is largely mediated via G-protein signaling, whereas adverse effects such as respiratory depression and PONV are often associated with β-arrestin pathway activation.[7] In recent years, the development of G-protein-biased μ-opioid receptor agonists has represented a significant advancement in opioid pharmacology. These agents selectively activate G-protein signaling, thereby providing effective analgesia while potentially mitigating typical ORAEs.[8]

Oliceridine, a novel G-protein-biased μ-opioid receptor agonist, represents a significant pharmacological advancement.[9] It is designed to provide analgesia while attenuating β-arrestin-mediated adverse effects.[10] Phase III clinical trials have demonstrated that oliceridine offers comparable analgesia to morphine with an improved tolerability profile, particularly concerning respiratory depression and gastrointestinal side effects.[11,12] Nevertheless, direct comparisons between oliceridine and potent conventional opioids like sufentanil, which is widely used for postoperative analgesia, remain limited. This evidence gap is especially relevant in patient populations at high risk for opioid-related adverse events, such as women undergoing laparoscopy hysterectomy, who frequently experience postoperative PONV and thus represent a special population.

We hypothesized that oliceridine would provide non-inferior analgesia to sufentanil while reducing the incidence of opioid-related adverse events in patients undergoing total laparoscopy hysterectomy. To test this hypothesis, we designed this prospective, randomized, double-blind controlled trial to compare the postoperative analgesic efficacy and safety profiles of oliceridine and sufentanil. The goal was to evaluate whether oliceridine can enhance postoperative recovery in women undergoing this procedure.

Materials and Methods

Study Design and Ethical Statements

This single-center, prospective, randomized, double-blind clinical trial was conducted in strict accordance with ethical guidelines for clinical research and conformed to the principles of the Declaration of Helsinki. The study protocol received ethical approval from the Ethics Committee of Anqing Municipal Hospital (Medical Ethics Approval No. 2025119). The trial was prospectively registered at the Chinese Clinical Trial Registry (Registration No. ChiCTR2500103115, Principal Investigator: Jinjuan Duan, Registration Date: May 26, 2025) prior to participant recruitment. All participants provided written informed consent before enrollment. Furthermore, this manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT)[13] guidelines. This adherence ensures transparent and comprehensive reporting of the trial methodology and results.

Study Population

Female patients scheduled to undergo elective total laparoscopy hysterectomy were enrolled in this study. The surgical indications encompassed benign conditions such as uterine fibroids or adenomyosis, as well as pre-malignant or early-stage malignant lesions including endometrial atypical hyperplasia, cervical intraepithelial neoplasia, or carcinoma in situ of the cervix. Eligible participants met the following criteria: Classified as American Society of Anesthesiologists (ASA) physical status I–III; Aged between 18 and 65 years; With a body mass index (BMI) ranging from 18 to 32 kg/m^2. All participants provided voluntary written informed consent, in compliance with ethical guidelines. The exclusion criteria were as follows: severe cardiac, pulmonary, hepatic, or renal dysfunction; a history of psychiatric disorders (eg, dementia, schizophrenia); chronic use of psychotropic or analgesic drugs; alcoholism; active infections of significant severity; communication impairments such as language barriers, hearing deficits, or cognitive dysfunction that precluded independent interaction; preoperative hypoxemia (PaO_2< 60 mmHg or SpO_2< 92%); and participation in another investigational drug trial within the preceding 30 days. Withdrawal criteria included the onset of serious adverse events,

conversion to open surgery, postoperative emergency reoperation, non-adherence to the study drug administration protocol, and inability to complete follow-up assessments.

Randomization and Masking

Randomization was performed using a computer-generated block randomization sequence (block size of 6, seed number: 20250530) created by an independent statistician using R statistical software version 4.5.0, ensuring a 1:1 allocation ratio between the oliceridine (Group O) and sufentanil (Group S) groups. Allocation concealment was maintained using sequentially numbered, opaque, tamper-proof envelopes securely stored by a research coordinator with no direct patient contact. Following standardized general anesthesia induction, the coordinator opened the sealed envelope in a secure monitoring room to disclose group assignment. An independent pharmacist, uninvolved in other trial procedures, prepared all study medications: identical 5-mL syringes for analgesic loading doses and 100-mL PCIA pumps for continuous infusion, labeled only with "Analgesic Loading Dose" or "Postoperative Analgesia Maintenance" without drug identity. All solutions were visually indistinguishable. Critically, all participants received identical preoperative instructions. This comprehensive design ensured true double-blinding: 1) participants remained unaware of intervention assignments; 2) anesthesiologists and surgeons were blinded to group allocation through neutral labeling and standardized protocols; and 3) outcome assessors and statisticians were blinded via concealed grouping and anonymized data, adhering to CONSORT criteria for double-blind trials.

Preoperative Management

An independent anesthesiologist, unaware of the allocation sequence, conducted preoperative assessments one day before surgery, during which the study procedures were outlined and standardized instructions on pain level measurement were delivered using the Numeric Rating Scale (NRS).

Anesthesia and Postoperative Analgesia Management

All patients followed standard preoperative fasting protocols, abstaining from solid foods for 8–12 hours and clear liquids for at least 2 hours. Upon arrival in the operating room, intravenous access was established, and routine monitoring was applied with MP40 Monitor (Philips, Germany), including electrocardiography (ECG), pulse oxygen saturation (SpO_2), non-invasive blood pressure (BP), and heart rate (HR). Preoxygenation was conducted via a face mask with an oxygen flow rate of 6–8 L/min for 5 minutes to achieve denitrogenation. Subsequently, intravenous ondansetron (Qilu Pharmaceutical Co., Ltd., China; NMPA Approval No. H10970062) 8 mg was administered prophylactically for postoperative nausea and vomiting. Anesthesia induction was standardized for both groups and included intravenous administration of midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H10980025) 0.05 mg/kg, cisatracurium (Zhejiang Xianju Pharmaceutical Co., Ltd. China; NMPA Approval No. H20090198) 0.1 mg/kg, remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H20143315) 1 μg/kg, and propofol (Yangtze River Pharmaceutical Co., Ltd., China; NMPA Approval No.: H20030113) 1–2 mg/kg. After the anesthesiologist confirmed adequate neuromuscular blockade, indicated by jaw relaxation, an appropriately sized laryngeal mask airway (LMA) was inserted. After verifying correct LMA placement, the anesthesiologist connected the device to the anesthesia machine. Ventilator parameters were set as follows: tidal volume 6–8 mL/kg; respiratory rate 12–15 breaths per minute; and an inspiratory-to-expiratory ratio of 1:2, with the goal of maintaining end-tidal carbon dioxide ($PetCO_2$) between 35–45 mmHg. Core body temperature was maintained within 36–37°C. Anesthesia maintenance was achieved with continuous infusions of propofol 4–8 mg/kg/h and remifentanil 0.1–0.3 μg/kg/min in both groups. Supplemental cisatracurium 1–2 mg was administered intermittently as required. The propofol infusion rate was titrated, targeting a bispectral index (BIS) value between 40–60. Intraoperative hypotension, defined as a reduction in BP exceeding 20% from baseline or a systolic blood pressure below 90 mmHg, was managed with intravenous phenylephrine 40 μg, or ephedrine 6 mg, guided by the patient's HR. Hypertension, defined as an increase in BP greater than 20% above baseline or systolic blood pressure exceeding 160 mmHg, was treated with urapidil or nitrendipine. Bradycardia, defined as a heart rate below 50 beats per minute, was addressed with intravenous atropine sulfate 0.3–0.5 mg.

For postoperative analgesia, after the specimen removal during laparoscopy surgery, patients in the group O received an intravenous loading dose of oliceridine (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H20233510) 0.05 mg/kg, followed by initiation of PCIA using a pump. The PCIA solution contained oliceridine 0.35 mg/kg diluted with normal saline to a total volume of 100 mL, administered at a basal rate of 2 mL/h, with a bolus dose of 0.5 mL per demand. Patients in the group S received an intravenous loading dose of sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd. China; NMPA Approval No. H20054171) 0.2 μg/kg, followed by initiation of PCIA with a pump containing sufentanil 2 μg/kg diluted with normal saline to 100 mL, delivered at a basal rate of 2 mL/h, and a bolus dose of 0.5 mL per demand.

Upon completion of the total laparoscopy hysterectomy, specifically after skin closure, the administration of remifentanil and propofol was terminated. The LMA was removed in the operating room or post-anesthesia care unit (PACU), based on the patient's recovery status. Criteria for LMA removal included patient alertness, responsiveness to verbal commands, and recovery of muscle strength. Patients were closely monitored in the operating room or the PACU for vital signs and adverse events, and transfered to the ward after achieving an aldrete score greater than 9. If the postoperative NRS score remained above 3, rescue analgesia was administered intravenously as tramadol at 1 mg/kg.

Outcome Measures

The primary outcome was the assessment of pain intensity during coughing at 6 hours postoperatively. It was evaluated in the ward using the Numeric Rating Scale (NRS)[14] by an independent assessor who was blinded to group allocation. The NRS scores range from 0 (indicating "no pain") to 10 (representing "the worst imaginable pain"). The secondary outcomes included the resting and coughing NRS pain scores assessed at 0.5, 2, 6, 12, 24, and 48 hours postoperatively, with the exclusion of the coughing NRS pain score at 6 hours postoperatively, which was designated as the primary outcome. All NRS assessments were performed by independent follow-up personnel blinded to group allocation, either in the operating room, post-anesthesia care unit (PACU), or on the ward, for a total of 12 evaluations. Other secondary outcomes were the number of PCIA pump presses postoperatively, the number of patients requiring rescue analgesia and the total dose of rescue analgesic medication administered within 48 hours; as well as time to first flatus and time to first ambulation; additionally, the Quality of Recovery-15 (QoR-15)[15] score at 24 hours postoperatively was assessed. The QoR-15 scale includes 15 items covering important dimensions such as pain, physical comfort, physical independence, psychological support, and emotional state. The assessment uses a scoring scale ranging from 0 to 10 points, where 0 points indicate "the worst state" and 10 points represent "the best state", with a total score range of 0 to 150 points. A higher score means better postoperative recovery quality.

Exploratory outcomes included HR and mean arterial pressure (MAP) at baseline prior to intravenous analgesic loading dose administration, and at 5, 15, and 30 minutes following the loading dose; as well as time to emergence and extubation.

Safety indicators included the incidence of adverse events within 48 hours postoperatively, such as respiratory depression during emergence (defined as occurring within half an hour after extubation, when the patient receives oxygen delivery via face mask at a flow rate of 5 L/min and SpO_2 remains below 92%), nausea and vomiting (PONV, defined as retching, vomiting, or both), drowsiness, pruritus, and rash.

Preoperative demographic data included age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, preoperative comorbidities, education level, and duration of surgery and anesthesia time.

Sample Size

To determine the required sample size, a pilot study involving 15 patients was conducted. It revealed a mean cough NRS score of 3.3±1.2 measured at 6 hours postoperative, and this mean score was designated as the primary outcome measure. Based on the pilot study results, assuming a clinically meaningful reduction of 1 point in the NRS score, sample size calculation was performed using PASS software, version 15 (NCSS LLC) with a two-sided significance level (α) of 0.05 and statistical power (1-β) of 90%. The analysis indicated that a minimum of 32 patients per group would be required to detect this difference. To account for a potential dropout rate of 20%, 40 patients were allocated to each group, resulting in a total sample size of 80 patients for this study.

Statistical Analysis

All statistical analyses were conducted using R software version 4.5.0. Data normality was assessed via the Shapiro–Wilk test. Normally distributed continuous variables, including age, BMI, surgical duration, anesthesia duration, emergence time, tracheal extubation time, first postoperative flatus and ambulation, QoR-15 at 24h postoperatively were presented as mean ± standard deviation and compared using independent samples *t*-tests. Non-normally distributed continuous variables, including counts of PCIA activation, estimated bleeding, blood transfusion, urine output, total fluid infusion, length of hospital stay, HR and MAP following intravenous analgesic loading doses, were reported as median with interquartile range (IQR) and analyzed with the Mann–Whitney *U*-test. Ordinal variables, including NRS scores, were summarized as median (IQR) and evaluated using the Wilcoxon rank-sum test due to their ordinal nature. Categorical variables, including ASA classification, comorbidities, and incidences of postoperative adverse events, were expressed as absolute frequencies and proportions (n (%)) and compared via Pearson's chi-square test, and continuity-corrected chi-square test was applied when expected cell counts were below 5. In all analyses, a two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

Demographic Data

A total of ninety potential candidates were rigorously screened for eligibility. Two patients were excluded: one with severe cardiac dysfunction and one on long-term analgesic medication; five patients did not meet the inclusion criteria; and three patients declined participation. This resulted in the enrollment of eighty eligible participants who were allocated via block randomization into two groups of forty each. The study cohort adhered strictly to the protocol requirements, demonstrating a 100% retention rate in both groups with no occurrence of serious adverse events (Figure 1). Comprehensive analysis of baseline characteristics revealed no statistically significant differences between the groups ($P > 0.05$); similarly, comparative assessment of intraoperative parameters confirmed equivalence, as detailed in Table 1.

Efficacy Outcomes

Analgesic Efficacy Outcomes: the primary outcome, the cough NRS score at 6 hours postoperatively, did not show a statistically significant difference between the two study groups ($P > 0.05$). Regarding the secondary outcomes, the resting pain scores and cough NRS scores at 0.5, 2, 12, 24, and 48 hours after surgery (excluding the primary outcome time point) were also comparable. No statistically significant intergroup differences were observed at any of these measured time points (all $P > 0.05$). The detailed data for all pain scores across the assessed time points are presented in Table 2.

Hemodynamic parameters: Following intravenous administration of the analgesic loading dose, both the oliceridine and sufentanil groups exhibited a declining trend in HR and MAP; however, the oliceridine group demonstrated a more gradual reduction in these parameters. Specifically, HR was significantly higher in the oliceridine group compared to the sufentanil group at 5, 10, 15, and 30 minutes after administration. Similarly, MAP values were significantly higher in the oliceridine group relative to the sufentanil group at the 10-, 15-, and 30-minute time points, as depicted in Figure 2.

In the evaluation of postoperative outcomes, no statistically significant differences were observed between the oliceridine and sufentanil groups in the anesthesia emergence time (9.80 ± 2.44 min vs 9.83 ± 2.30 min, $P = 0.962$), tracheal extubation time (12.33 ± 2.57 min vs 12.58 ± 3.29 min, $P = 0.706$), number of PCIA attempts within 48 hours (3.00 [2.00, 4.00] vs 3.00 [1.25, 4.00], $P = 0.663$), proportion of patients requiring rescue analgesia (20.0% vs 17.5%, $P = 0.775$), the dosage of rescue tramadol administered (62.63 ± 4.53 mg vs 63.86 ± 4.30 mg, $P = 0.600$), or hospital length of stay (8.00 [7.00, 9.00] days vs 8.00 [6.25, 9.00] days, $P = 0.926$); however, the oliceridine group exhibited significantly earlier time to first ambulation (17.95 ± 3.30 hours vs 20.28 ± 3.76 hours, $P = 0.004$) and time to first flatus ((18.63 ± 3.51 hours vs 24.70 ± 3.26 hours, $P < 0.001$)), along with a significantly higher QoR-15 score (120.85 ± 7.15 vs 115.63 ± 6.74, $P = 0.001$) on 24h postoperatively, with comprehensive data detailed in Table 3.

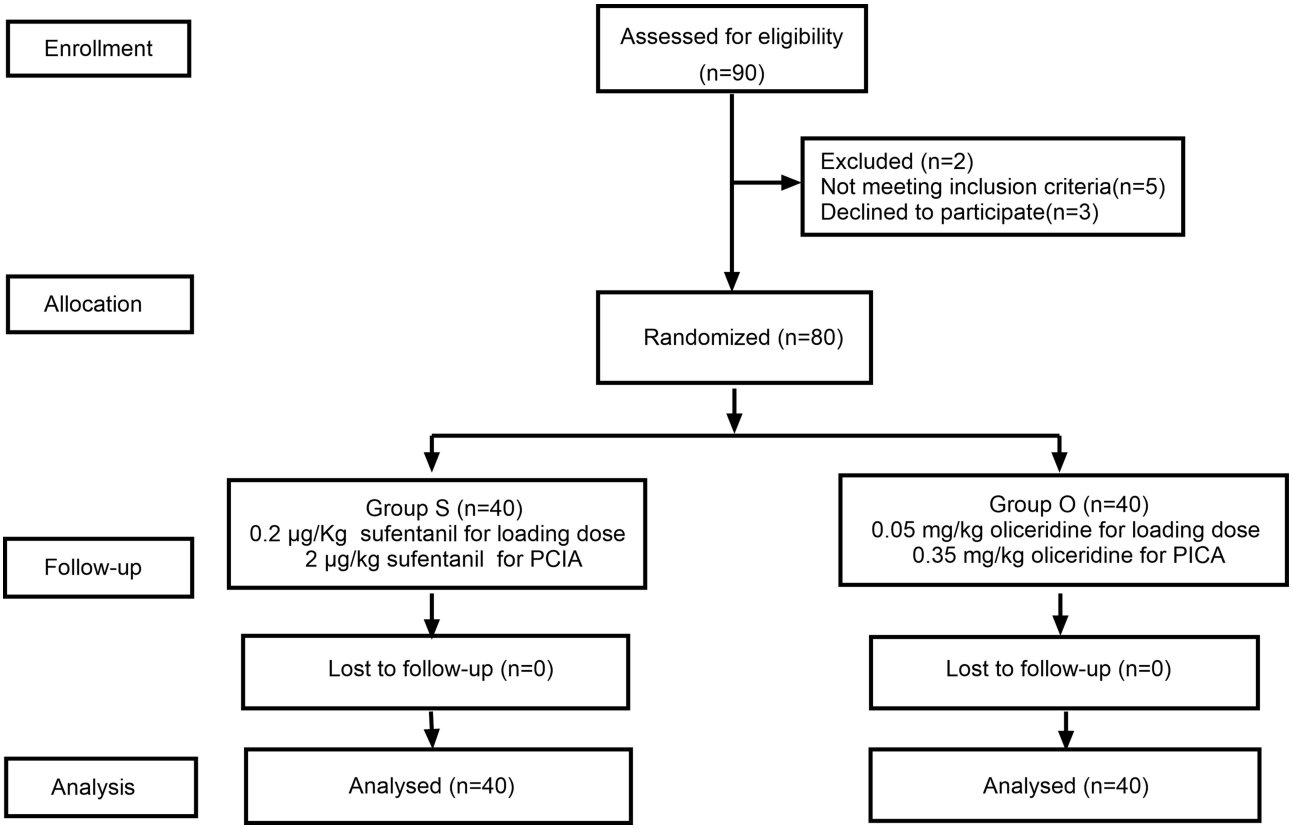

Figure 1 Study flow diagram. Ninety patients were initially enrolled, of whom two were excluded: one with severe cardiac dysfunction and one on long-term analgesic medication; five patients did not meet the inclusion criteria; and three patients declined participation. This resulted in the enrollment of eighty eligible participants (40 per group) were randomized and ultimately completed the trial, as detailed in the CONSORT-compliant flow diagram.

Safety Outcomes

Analysis of postoperative adverse events revealed significant intergroup differences in safety profiles. The oliceridine group demonstrated superior safety outcomes compared to the sufentanil group, with substantially lower incidence of

Table 1 Baseline Data

Variables	Group S (n=40)	Group O (n=40)	*P* value
Age, yr	49.38±5.43	51.00±5.53	0.189[a]
BMI, kg/m^2	23.78±3.09	24.62±2.60	0.192[a]
ASA			0.752[b]
I, n (%)	7(17.5%)	8(20.0%)	
II, n (%)	28(70.0%)	25(62.5%)	
III, n (%)	5(12.5%)	7(17.5%)	
Level of education, n (%)			0.805[b]
Primary school, n (%)	6(15.0%)	8(20.0%)	
Middle school, n (%)	16(40.0%)	12(30.0%)	
High school, n (%)	13(32.5%)	14(35.0%)	
College or higher, n (%)	5(12.5%)	6(15.0%)	
Principal diagnosis, n (%)			
Uterine fibroids, n (%)	11(27.5%)	9(22.5%)	0.606[b]
Adenomyosis, n (%)	8(20.0%)	9(22.5%)	0.785[b]

(*Continued*)

Table 1 (Continued).

Variables	Group S (n=40)	Group O (n=40)	*P* value
Endometrial atypical hyperplasia, n (%)	7(17.5%)	5(12.5%)	0.531[b]
Cervical intraepithelial neoplasia, n (%)	4(10.0%)	6(15.0%)	0.499[b]
Carcinoma in situ of the cervix, n (%)	5(12.5%)	6(15.0%)	0.745[b]
Other etiologies, n (%)	5(12.5%)	5(12.5%)	>0.999[b]
Comorbidity, n (%)			
Motion sickness, n (%)	11(27.5%)	13(32.5%)	0.626[b]
Anaemia, n (%)	9(22.5%)	10(25.0%)	0.793[b]
Chronic smoking, n (%)	6(15.0%)	4(10.0%)	0.499[b]
Hypertension, n (%)	5(12.5%)	6(15.0%)	0.745[b]
Coronary heart disease, n (%)	5(12.5%)	4(10.0%)	0.723[b]
Diabetes, n (%)	5(12.5%)	5(12.5%)	>0.999[b]
Operation duration, min	109.43±28.07	107.63±30.00	0.782[a]
Anesthesia duration, min	130.63±34.87	127.25±35.45	0.669[a]
Estimated bleeding, mL	50(50,100)	50(50,100)	0.799[c]
Blood transfusion, mL	0	0	>0.999[c]
Urine output, mL	300(200,370)	300(200,400)	0.783[c]
Total fluid infusion, mL	1000(500,1000)	1000(500,1000)	0.425[c]

Notes: Date are presented as mean ± SD, median (interquartile range), or number (percentage). Statistical tests for *P*-value calculation: [a]Independent samples *t*-test, [b]Pearson's chi-squared test, [c]Mann–Whitney *U*-Test.
Abbreviations: Group S, sufentanil group; Group O, oliceridine group; ASA, American Society of Anesthesiologists.

Table 2 Postoperative Numerical Rating Scale (NRS) Score

Variables	Group S (n=40)	Group O (n=40)	*P* value
0.5 h rest NRS	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.912[a]
2 h rest NRS	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.628[a]
6 h rest NRS	2.00 (1.00, 2.00)	2.00 (2.00, 2.00)	0.201[a]
12 h rest NRS	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	0.388[a]
24 h rest NRS	2.00 (1.00, 2.00)	2.00 (2.00, 2.00)	0.125[a]
48 h rest NRS	1.00 (1.00, 1.00)	1.00 (1.00, 1.75)	0.267[a]
0.5 h cough NRS	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.203[a]
2 h cough NRS	2.00 (1.00, 2.00)	2.00 (2.00, 2.00)	0.160[a]
6 h cough NRS	2.00 (2.00, 3.00)	2.50 (2.00, 3.00)	0.519[a]
12 h cough NRS	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	0.848[a]
24 h cough NRS	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	0.734[a]
48 h cough NRS	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	0.191[a]

Notes: Date are presented median (interquartile range). Statistical tests for *P*-value calculation: [a]Wilcoxon rank-sum test.
Abbreviations: Group S, sufentanil group; Group O, oliceridine group; NRS, Numerical Rating Scale (0 = no pain to 10 = worst pain).

overall postoperative adverse events (32.5% vs 62.5%, $P = 0.007$), this is particularly evident in the pronounced decrease in respiratory depression during emergence (5.0% vs 22.5%, $P = 0.023$) and the lower frequency of PONV episodes (17.5% vs 40.0%, $P = 0.026$). Although somnolence occurred less frequently in oliceridine group (15.0% vs 22.5%, $P = 0.390$), this difference did not reach statistical significance. Similarly, the incidences of dizziness (6.7% vs 10.0%, $P = 0.709$), chest tightness (2.5% vs 5.0%, $P > 0.999$), and dermatological manifestations including rash (2.5% vs 2.5%, $P > 0.999$) and pruritus (0.0% vs 2.5%, $P > 0.999$) were consistently lower in the oliceridine cohort, though these reductions were not statistically significant. These comprehensive safety outcomes are systematically detailed in Table 4.

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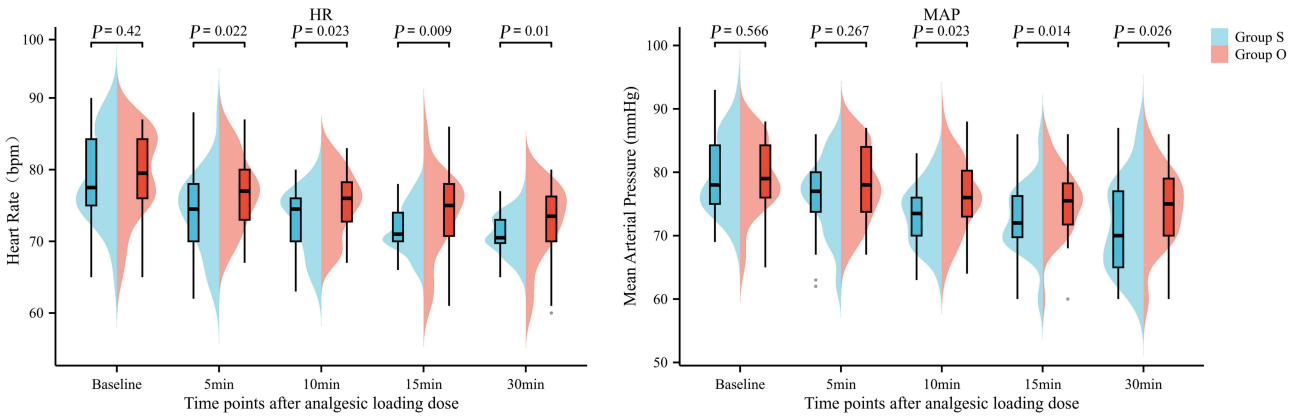

Figure 2 The comparative analysis of hemodynamic parameters following intravenous analgesic loading dose administration in the oliceridine group and sufentanil group. Both the oliceridine and sufentanil groups exhibited a declining trend in HR and MAP. However, the oliceridine group demonstrated a more gradual reduction in these parameters. Specifically, HR was significantly higher in the oliceridine group compared to the sufentanil group at 5, 10, 15, and 30 minutes after administration. Similarly, MAP values were significantly higher in the oliceridine group relative to the sufentanil group at the 10-, 15-, and 30-minute time points; All hemodynamic parameters were analyzed using the Mann–Whitney *U*-Test, with *P*-values explicitly annotated in the figure.
Abbreviations: Group S, sufentanil group; Group O, oliceridine group; HR, heart rate; MAP, mean arterial pressure.

Discussion

The present double-blind, randomized controlled trial provides compelling evidence that oliceridine, a novel μ-opioid receptor agonist with biased G-protein signaling, demonstrates comparable analgesic efficacy to sufentanil in patients

Table 3 Postoperative Outcomes

Variables	Group S (n=40)	Group O (n=40)	*P* value
Time to awareness, min	9.80±2.44	9.83±2.30	0.962[a]
Time to extubation, min	12.33±2.57	12.58±3.29	0.706[a]
Counts of PCIA activation, times	3.00 (1.25,4.00)	3.00 (2.00,4.00)	0.663[b]
Postoperative analgesic remedy, n (%)	7 (17.5%)	8 (20.0%)	0.775[c]
Postoperative tramadol consumption, mg	63.86 ± 4.30	62.63 ± 4.53	0.600[a]
First postoperative flatus, h	24.70 ± 3.26	18.63 ±3.51**	<0.001[a]
First postoperative ambulation, h	20.28 ± 3.76	17.95 ± 3.30**	0.004[a]
QoR-15 at 24h postoperatively, points	115.63 ± 6.74	120.85 ± 7.15**	0.001[a]
Length of hospital stay, days	8.00 (6.25,9.00)	8.00 (7.00,9.00)	0.926[b]

Notes: Date are presented as mean ± SD, median (IQR), or number (percentage). ***P* <0.01. Statistical tests for *P*-value calculation: [a]Independent samples *t*-test, [b]Mann–Whitney *U*-test, [c]Pearson chi-square test.
Abbreviations: Group S, sufentanil group; Group O, oliceridine group; QoR-15, 15-item Quality of Recovery scale (overall score ranges from 0 to 150, with a higher score indicating better postoperative recovery).

Table 4 Safety Outcomes

Variables	Group S (n=40)	Group O (n=40)	*P* value
Total number of patients with postoperative adverse events, n (%)	25(62.5%)	13(32.5%)**	0.007[a]
Respiratory depression during emergence, n (%)	9(22.5%)	2(5.0%)*	0.023[a]
Nausea/Vomiting, n (%)	16(40.0%)	7(17.5%)*	0.026[a]
Somnolence, n (%)	9(22.5%)	6(15.0%)	0.390[a]
Dizziness, n (%)	5(10.0%)	3(6.7%)	0.709[b]
Chest tightness, n (%)	2(5.0%)	1(2.5%)	>0.999[b]
Rash, n (%)	1(2.5%)	1(2.5%)	>0.999[b]
Pruritus, n (%)	1(2.5%)	0(0.0%)	>0.999[b]

Notes: Date are presented as number (percentage). **P*<0.05; ***P*<0.01. Statistical tests for *P*-value calculation: [a]Pearson's chi-squared test; [b]Chi-square test with continuity correction.
Abbreviations: Group S, sufentanil group; Group O, oliceridine group.

undergoing total laparoscopy hysterectomy, while offering distinct advantages in hemodynamic stability, postoperative recovery, and safety profile. Our findings contribute to the growing body of literature supporting the clinical utility of oliceridine as a potentially superior alternative to conventional opioids in perioperative pain management.

The analysis of postoperative analgesic outcomes demonstrated non-inferiority of oliceridine compared to sufentanil, as evidenced by the absence of statistically significant differences in NRS scores at rest and during coughing at all time points over the 48-hour postoperative period, along with comparable PCIA activation counts, proportion of patients requiring rescue analgesia, and rescue analgesic dose between the two groups. These findings align with prior research indicating that oliceridine provides potent analgesia equivalent to conventional opioids,[16–18] mechanistically attributed to its selective activation of G-protein coupled signaling pathways, which facilitates pain inhibition similar to that of sufentanil. Furthermore, the lack of disparity in anesthesia emergence and tracheal extubation times suggests that oliceridine does not adversely affect anesthesia emergence. Nonetheless, these findings are confined to total laparoscopy hysterectomy, limiting generalizability; the extrapolation of oliceridine's efficacy to major surgeries involving extensive tissue damage, heightened stress responses, and complex pain mechanisms necessitates further empirical validation.

The hemodynamic analysis in this study revealed that both oliceridine and sufentanil groups exhibited reductions in HR and MAP following intravenous administration of the analgesic loading dose, which may be attributed to enhanced analgesic efficacy and increased anesthetic depth attenuating stress-induced cardiovascular responses, thereby leading to cardiovascular depression. Notably, the oliceridine group demonstrated a statistically significant smaller magnitude of decline in both parameters compared to the sufentanil group, indicating a milder cardiovascular depressive effect with oliceridine, which is consistent with the previous research findings of Chen et al.[19] This differential effect may stem from traditional opioids like sufentanil recruiting β-arrestin, potentially suppressing the autonomic nervous system and compromising baroreflex-mediated compensatory mechanisms during nociceptive stimuli,[20] in contrast, the G protein bias of oliceridine maintains autonomic tone,[8] as evidenced by the cardiovascular metrics observed herein in this trial. These findings underscores oliceridine's potential for superior clinical safety, particularly in patients with compromised cardiovascular systems, by mitigating excessive hemodynamic instability while maintaining effective analgesia.

A key finding of this study was the significantly earlier time to first ambulation and first flatus in the oliceridine group, alongside superior QoR-15 scores on postoperative 24 hours. These outcomes suggest that oliceridine may facilitate faster gastrointestinal recovery and functional mobilization, which can be mechanistically explained by oliceridine's profile as a G protein-biased μ-opioid receptor agonist that preferentially activates G protein signaling while minimizing β-arrestin recruitment.[21–23] This biased agonism results in effective analgesia with attenuated μ-receptor-mediated adverse effects, such as postoperative PONV and somnolence,[24,25] thereby promoting earlier ambulation by reducing discomfort and enhancing patient willingness to mobilize. Simultaneously, the diminished β-arrestin engagement reduces gastrointestinal inhibitory effects,[26] accelerating the return of bowel function and explaining the shorter time to first flatus. Collectively, these mechanisms underpin the superior recovery quality observed with oliceridine, aligning with enhanced recovery after surgery (ERAS) principles and potentially contributing to more efficient postoperative rehabilitation, though our study did not detect a significant difference in length of stay, possibly due to institutional discharge protocols.

The oliceridine group demonstrated a markedly lower incidence of overall adverse events (32.5.0% vs 62.5%, $P = 0.007$), with lower frequency of respiratory depression during emergence (5.0% vs 22.5%, $P = 0.023$) and PONV (17.5% vs 40.0%, $P=0.026$) being significantly less frequent. This aligns with previous reports of oliceridine's reduced respiratory depression and emetogenic potential compared to traditional opioids.[27–29] While dizziness, somnolence, and dermatological reactions were numerically less common with oliceridine, these differences did not reach statistical significance, possibly due to sample size limitations. Nevertheless, the trend toward fewer opioid-related side effects reinforces the hypothesis that G-protein-biased agonists may offer a safer therapeutic window by mitigating β-arrestin-mediated adverse effects.[30,31]

This study has several limitations that should be acknowledged, including a relatively small sample size of 80 patients, which may limit the statistical power to detect minor differences in pain scores or other secondary outcomes. The single-center design and focus on elective total laparoscopy hysterectomy may restrict the generalizability of findings to other surgical populations or healthcare settings. The assessment of adverse events was confined to 48 hours postoperatively, potentially overlooking late-onset complications or longer-term recovery issues. The focus

on specific postoperative time points may not fully capture dynamic pain or functional changes, and the absence of long-term follow-up prevents evaluation of sustained recovery benefits. Additionally, while standardized protocols were used, potential unmeasured confounding factors, such as variations in surgical technique or individual pain thresholds, could influence outcomes. Future multi-center trials with larger cohorts and extended observation periods are needed to validate these findings and explore broader applications.

Conclusion

This trial demonstrates that oliceridine provides analgesia equivalent to sufentanil in total laparoscopy hysterectomy while offering superior hemodynamic stability, faster postoperative recovery, and a more favorable safety profile. These advantages, coupled with its mechanistic novelty, underscore oliceridine's potential as a first-line opioid in enhanced recovery pathways. Further research should investigate its long-term benefits and cost-effectiveness in diverse surgical populations. Additionally, multicenter studies with a large number of patients are needed.

Data Sharing Statement

The datasets used and analyzed during the current study are available from corresponding author Siqi Xu (Email: errtg555@163.com) upon reasonable request.

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Disclosure

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