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CLINICAL TRIAL REPORT

Comparison of Oliceridine and Morphine in Postoperative Analgesia in Laparoscopic Total Hysterectomy, a Randomized Double-Blind Controlled Trial

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Purpose: Compare the analgesic efficacy and safety profiles of oliceridine and morphine in patient-controlled intravenous analgesia (PCIA) after laparoscopic total hysterectomy.

Materials and Methods: This prospective, double-blind trial randomly allocated 60 patients undergoing elective laparoscopic total hysterectomy in a 1:1 ratio to receive either oliceridine (group O) or morphine (group M) via PCIA. The primary endpoint was cough numerical rating scale (NRS) scores 6 h postoperatively. Secondary outcomes included cough/resting NRS scores at 0.5, 2, 6, 12, 24, and 48 h (6 h cough NRS score excluded); 24-hour postoperative recovery quality using 15-item Quality of Recovery (QoR-15) scale. Exploratory indicators including hemodynamic parameters and peripheral capillary oxygen saturation (SpO_2) post intravenous analgesic loading dose. Safety indicators represented by the incidence of adverse events occurring within 72 hours postoperatively.

Results: Group O demonstrated superior early analgesia with lower resting NRS (1.0 [1.0,1.0] vs 1.5 [1.0,2.0]; $P = 0.019$) and cough NRS (1.0 [1.0–2.0] vs 2.5 [1.0–3.0]; $P = 0.003$) at 0.5 h compared with group M, and analgesic efficacy was comparable thereafter (all $P > 0.05$). Group O exhibited lower nausea/vomiting (33.3% vs 73.3%, $P = 0.002$) and constipation (20.0% vs 53.3%, $P = 0.007$) rates, along with higher 24-h QoR-15 scores (125.27 ± 10.11 vs 119.67 ± 8.49; $P = 0.024$). Higher SpO_2 in group O at 5 min ($P = 0.003$) and 10 min ($P = 0.033$) postloading doses. Meanwhile, group M demonstrated transient heart rate (HR) elevation at 5 min postloading dose, whereas group O exhibited no significant HR increases at any time point.

Conclusion: Oliceridine demonstrates analgesic efficacy comparable to morphine after laparoscopic total hysterectomy but exhibits superior safety by significantly reducing opioid-related adverse events and potentially accelerating postoperative recovery.

Keywords: oliceridine, morphine, biased μ-opioid receptor agonist, postoperative analgesia, opioid-related adverse events, laparoscopic total hysterectomy

Introduction

Postoperative pain, which affects more than 80% of patients undergoing surgery, with 75% and even more of them reporting moderate-to-severe intensity,[1] represents a crucial challenge in perioperative care. Inadequate pain management is associated with impaired functional recovery, prolonged hospitalization, and increased healthcare costs.[2–4] Patient-controlled intravenous analgesia (PCIA) has become a cornerstone modality, providing procedural simplicity and sustained analgesic duration.[5] PCIA optimizes pain control by enabling demand-adjusted dosing while mitigating stress response and hemodynamic fluctuations.[6]

Morphine remains the archetypal opioid for PCIA, exhibiting potent μ-opioid receptor (MOR) agonism. However, the clinical utility of morphine, as a prototypical μ-opioid receptor agonist, is constrained by dose-dependent adverse effects

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such as nausea/vomiting or respiratory depression.[7] Traditional MOR agonists nonselectively activate both the G-protein and β-arrestin pathways.[8] G-protein coupling mediates analgesia, whereas β-arrestin signaling drives opioid-related adverse events (ORAEs) such as respiratory suppression and gastrointestinal dysmotility.[9–11]

Oliceridine, which is a novel MOR-biased ligand, selectively engages G-protein signaling (β-arrestin recruitment <10% vs morphine) through optimized receptor phosphorylation kinetics.[12] This mechanistic divergence translates into comparable analgesia with improved safety, lower nausea risk, and reduced oxygen desaturation events.[13] Phase III trials (APOLLO) have established oliceridine's theoretical advantages;[14–16] however, its clinical translation in gynecological populations—particularly those undergoing laparoscopic total hysterectomy with unique pain trajectories[17] and high ORAE incidences[18]—remains underexplored.

We hypothesize that oliceridine-based PCIA achieves non-inferior analgesia compared with morphine while significantly reducing ORAEs and improving postoperative recovery quality in this population.

To address this evidence gap, we conducted this randomized controlled trial and provided novel information about the use of oliceridine, which is a μ-opioid receptor agonist with biased signaling properties, and compared it with morphine, which is the long-standing gold standard, in PCIA after laparoscopic total hysterectomy. This study aimed to identify safer and more effective postoperative analgesic methods for patients undergoing laparoscopic total hysterectomy to promote improved recovery.

Materials and Methods

Study Design and Ethical Statements

This single-center, prospective, randomized, double-blind clinical trial was conducted under the ethical standards of clinical research. The Institutional Review Board of Anqing Hospital affiliated with China Pharmaceutical University granted ethical approval for this study (Medical Ethics Approval No. 2024075). The trial protocol was prospectively registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR2400086706; principal investigator: Jinjuan Duan; registration date: July 9, 2024) before participant enrollment. All participants signed written informed consent before any study-related procedures. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT)[19] guidelines, ensuring complete and transparent reporting of all trial methodology and results.

Selection of Study Population

This prospective trial enrolled patients with American Society of Anesthesiologists physical status of I–II, ages of 18–65 years, body mass index of 18–35 Kg/m², and weight of >40 kg who underwent elective laparoscopic total hysterectomy with written informed consent obtained under Institutional Review Board supervision. The exclusion criteria were significant cardiopulmonary/hepatorenal dysfunction (New York Heart Association Functional classification of ≥III, chronic obstructive pulmonary disease, Child-Pugh classification of ≥B, and estimated glomerular filtration rate of <30 mL/min/1.73 m²), active systemic infection (temperature of >38.5°C with a leukocyte count of >12 × 10^9/L), neuropsychiatric comorbidities (dementia, schizophrenia, and chronic psychotropic/analgesic use of >3 months), communication-impairing neurological deficits (stroke sequelae and aphasia), preoperative hypoxemia (PaO_2 of <60 mmHg/ SpO_2 of <92% on room air), and recent participation in other drug trials (≤30 days). Protocol deviations mandated discontinuation for hypersensitivity reactions, hemorrhage of >800 mL, unplanned reoperations, nonadherence to analgesic protocols, or failure to complete 72-hour postoperative assessments.

Randomization and Masking

An independent statistician computer-generated the randomization sequence using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) with block design (block size = 4), ensuring 1:1 allocation between the oliceridine (group O) and morphine (group M) arms. Allocation concealment was rigorously maintained using sequentially numbered, opaque, tamper-evident envelopes that a research coordinator, who had no participant contact, had stored. After standardized general anesthesia induction, the coordinator accessed the sealed envelope in a secured monitoring room to preserve chronological integrity. An independent pharmacist (with no other trial involvement) prepared identical 5-mL syringes containing either 1.5 mg of oliceridine or 4 mg of morphine in normal saline, labeled only as "loading dose" without drug

identifiers. Weight-adjusted PCIA pumps were preloaded with allocated opioids in indistinguishable reservoirs through these procedures. The visual indistinguishability of all investigational drugs was ensured. Crucially, all participants received identical preoperative instructions. This comprehensive design ensured authentic double-blinding as follows. 1) Participants were blinded to pharmacological intervention. 2) Anesthesiologists/surgeons were blinded to neutral drug labeling and standardized protocols. 3) Outcome assessors and statisticians remained blinded to allocation concealment and data anonymization, thereby fulfilling the CONSORT criteria for double-blind trials.

Preoperative Management

A separate anesthesiologist, blinded to the randomization sequences, performed preoperative visits 24 h preoperatively to explain the study protocol and provide standardized training on pain intensity quantification using the NRS (0 = no pain to 10 = worst pain).

Anesthesia and Postoperative Analgesia Management

All patients received no preoperative medications and adhered to standardized fasting guidelines: 8–12 h for solids and ≥2 h for clear fluids. Intravenous (IV) access is secured upon arrival in the operating suite. Subsequently, continuous monitoring with electrocardiogram, SpO_2, noninvasive blood pressure (NIBP), and nasopharyngeal temperature was performed using the MP40 Patient Monitor (Philips, Germany). Preoxygenation was administered via a tight-sealing face mask with 100% oxygen at a 6–8 L/min flow rate for 5 min to achieve adequate denitrogenation. A modified rapid sequence induction protocol was implemented, including an initial administration of 0.02 mg/Kg of midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H10980025), 0.1 μg/Kg of sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd. China; NMPA Approval No. H20054171), and 0.02 mg/Kg of cisatracurium besylate (Zhejiang Xianju Pharmaceutical Co., Ltd. China; NMPA Approval No. H20090198), followed by 5 min of continued oxygenation. Subsequent induction agents included 0.03 mg/kg of midazolam, 0.03 mg/kg of etomidate (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H32022992), 0.4 μg/kg of sufentanil, and 0.1 mg/kg of cisatracurium besylate. Notably, no positive-pressure ventilation was applied during induction. Orotracheal intubation was performed upon achieving a complete neuromuscular blockade (mandibular relaxation). We then connected the anesthesia machine (Dräger Fabius® Plus, Germany), and mechanical ventilation parameters were standardized to tidal volume of 6–8 mL/kg, respiratory rate of 12–15 breaths/min, I:E ratio of 1:2, with a perioperative fraction of inspired oxygen (FiO_2), maintained at 50%, targeting pressure of end-tidal carbon dioxide ($PetCO_2$) of 35–45 mmHg. The nasopharyngeal temperature was maintained within the normothermic range (36.0°C–37.0°C) throughout the procedure.

Anesthesia maintenance was achieved through continuous infusions of propofol (Yangtze River Pharmaceutical Co., Ltd., China; NMPA Approval No.: H20030113) at 4–8 $mg \cdot kg^{-1} \cdot h^{-1}$ and remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; NMPA Approval No. H20143315) at 0.1–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with supplemental cisatracurium (1–2 mg of boluses) administered as required. Hemodynamic stability was actively managed. Hypotension (defined as systolic blood pressure [SBP] of <90 mmHg or >20% below baseline) was treated with phenylephrine of 40 μg (heart rate [HR] >60 bpm) or ephedrine of 6 mg (HR ≤60 bpm); whereas, hypertension (SBP of >160 mmHg or >20% above baseline) was addressed with urapidil of 15 mg. Bradycardia (HR <50 bpm) was corrected with IV atropine of 0.3–0.5 mg.

Anesthetic agents were discontinued at skin closure. After surgery completion, patients were transferred to the postanesthesia care unit (PACU). The extubation criteria included restoring muscle strength and consciousness of patients, clearing airway secretions, performing manual lung expansion, following the endotracheal tube removal, and administering oxygen via face mask at a 5 L/min flow rate. Oxygen administration was discontinued after 5 min, and postoperative analgesia was initiated.

Postoperative analgesia protocols differed between the two groups. Group O received 1.5 mg of oliceridine as a loading dose, followed by PCIA with 0.35 mg/kg of oliceridine in 100 mL of normal saline (2 mL/h basal rates, 0.5 mL bolus, 15 min lockout); whereas group M received a 4 mg morphine loading dose with PCIA containing 1 mg/kg of morphine in 100 mL of normal saline (2 mL/h of basal rate, 0.5 mL of bolus, 15 min lockout). All patients were

monitored in the PACU until they achieved steward recovery scores of >4. Finally, the patient was transferred back to the ward. Tramadol (1 mg/kg) was IV administered as a rescue analgesia regimen.

Outcome Measures

The primary endpoint was cough-provoked pain intensity assessed using the NRS scores[20] at 6 h postoperatively. Secondary outcomes were categorized into three mechanistic domains. 1) Analgesic trajectory: cough-provoked NRS scores at 0.5, 2, 12, 24, and 48 h; resting NRS scores at 0.5, 2, 6, 12, 24, and 48 h; rescue analgesia incidence within 48 h. 2) Recovery metrics: postoperative recovery quality at 24 h assessed using the validated 15-item quality of recovery scale[21] (QoR-15, overall score ranges from 0 to 150, with a higher score indicating better postoperative recovery). 3) Safety profile: 72-h postoperative adverse events, including nausea/vomiting, sedation, pruritus, and constipation (failure to pass stool within 72 h). SpO_2 monitoring was retained only at 30 min postloading dose as a pharmacodynamic safety checkpoint. All intraoperative timelines (operation duration, anesthesia duration, time to awareness, and time to extubation) and hemodynamic parameters (HR, MAP, SBP, and diastolic blood pressure) were reclassified as exploratory variables, as they represent standard anesthesia monitoring rather than hypothesis-related endpoints. This refined structure ensured that all reported outcomes directly addressed the study's dual objectives, including comparative opioid efficacy and recovery quality assessment.

Sample Size

To identify the sample size required for the primary outcome, we conducted a pilot study that involved 10 patients in whom the mean cough NRS score at 6 h postoperatively was 3.5 ± 1.1. The calculated minimum sample size was 27 patients per group assuming a clinically meaningful difference of 1-point reduction in NRS scores and using PASS version 15 software (NCSS LLC) with a two-sided α of 0.05 and β of 0.1 (power = 90%). We ultimately enrolled 30 patients in each group to account for the potential 10% attrition rate.

Statistical Analysis

IBM Statistical Package for the Social Sciences Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. The normality of data distribution was assessed with Shapiro–Wilk testing. Continuous variables with normal distribution were expressed as mean ± standard deviation. These parameters were compared using independent samples *t*-tests. Non-normally distributed data (eg, SPO2 after IV analgesic loading doses) were presented as median (interquartile range [IQR]) and analyzed with Mann–Whitney *U*-tests. Ordinal categorical variables, such as NRS scores, were presented as median (IQR) and assessed using the Wilcoxon rank-sum test, consistent with their hierarchical distributional properties. Greenhouse–Geisser corrected repeated measure analysis of variance was employed to compare hemodynamic parameters across time points within the group. Nominal categorical variables (eg, postoperative adverse event incidence) were expressed as absolute frequencies with proportional representations (n[%]) and compared using Pearson's Chi-squared test or Chi-square test with continuity correction when cell expectations were below 5. A two-tailed *P*-value of <0.05 indicated statistical significance.

Results

Demographic Data

After the rigorous screening of 70 potential candidates, of whom 6 were excluded for failure to meet inclusion criteria and 4 declined participation, this randomized controlled trial ultimately enrolled 60 eligible participants (30 per arm) through computerized block randomization, as delineated in the CONSORT-compliant flowchart (Figure 1). The study cohort maintained strict protocol adherence with complete retention (100% compliance) and the absence of serious adverse events in both interventional groups. A comprehensive analysis of baseline characteristics revealed no statistically significant intergroup disparities ($P > 0.05$). Similarly, a comparative assessment of intraoperative parameters demonstrated equivalence between the groups (Table 1).

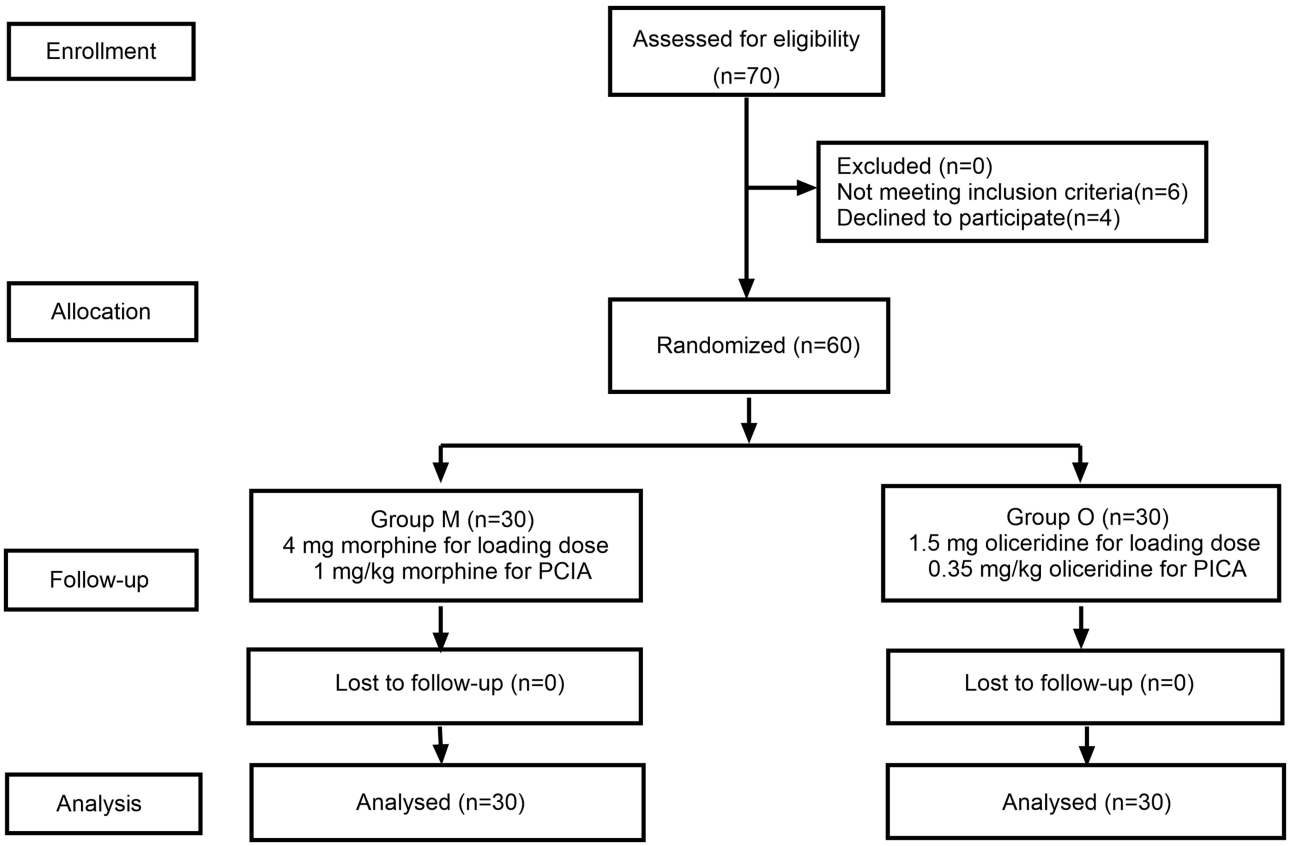

Figure 1 Study flow diagram. 70 patients were initially enrolled, of whom 6 were excluded for failure to meet inclusion criteria and 4 declined participation. The remaining 60 patients (30 per group) were randomized and ultimately completed the trial, as detailed in the CONSORT-compliant flow diagram.

Efficacy Outcomes

Comparative analyses of postoperative NRS scores between the groups revealed that group O demonstrated statistically significant superiority at two-time points: resting scores at 0.5 h postoperatively (1.0 [1.0, 1.0] vs 1.5 [1.0, 2.0] in group M; $P = 0.019$]) and cough scores at 0.5 h (1.0 [1.0, 2.0] vs 2.5 [1.0, 3.0]; $P = 0.003$), with median differences of 0.5 and 1.5 points, respectively. No other temporal intervals exhibited statistically discernible intergroup differences (all $P > 0.05$; Table 2).

Table 1 Baseline Data

Variables	Group M (n=30)	Group O (n=30)	*P* value
Age, yr	49.00±5.25	49.00±6.05	>0.999[a]
BMI, kg/m^2	24.14±2.41	23.74±2.66	0.541[a]
ASA			0.595[b]
I, n (%)	20(66.7%)	18(60.0%)	
II, n (%)	10(33.3%)	12(40.0%)	
Level of education, n (%)			0.549[b]
Primary school, n (%)	7(23.3%)	5(16.7%)	
Middle school, n (%)	10(33.3%)	11(36.7%)	
High school, n (%)	8(26.7%)	7(23.3%)	
College or higher, n (%)	5(16.7%)	7(23.3%)	
Comorbidity, n (%)			
Hypertension, n (%)	5(16.7%)	8(26.7%)	0.347[c]
Coronary heart disease, n (%)	3 (10%)	2(6.7%)	>0.999[d]

(*Continued*)

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Table 1 (Continued).

Variables	Group M (n=30)	Group O (n=30)	*P* value
Sinus Bradycardia, n (%)	1 (3.3%)	1 (3.3%)	>0.999[d]
Diabetes, n (%)	0(0.0%)	2(6.7%)	0.472[d]
Anaemia, n (%)	3(10.0%)	1(3.3%)	0.605[d]
Chronic smoking, n (%)	2(6.7%)	4(13.3%)	0.667[d]
Operation duration, min	100.67±21.36	101.07±23.59	0.945[a]
Anesthesia duration, min	115.67±20.58	115.23±22.22	0.938[a]
Time to awareness, min	6.93±1.70	7.00±1.66	0.878[a]
Time to extubation, min	8.57±1.72	8.73±1.72	0.709[a]
Estimated bleeding, mL	50(50,100)	50(50,100)	0.757[b]
Blood transfusion, mL	0	0	>0.999[b]
Urine output, mL	200(200,300)	200(200,300)	0.728[b]
Total fluid infusion, mL	900(800,1000)	900(800,1000)	0.360[b]

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]Mann–Whitney *U*-test, [c]Pearson's chi-squared test, [d]Chi-square test with continuity correction.
Abbreviations: Group M, morphine group; Group O, oliceridine group; ASA, American Society of Anesthesiologists.

Table 2 Postoperative Numerical Rating Scale (NRS) Scores

Variables	Group M (n=30)	Group O (n=30)	*P* value
0.5 h rest NRS	1.5 (1.0, 2.0)	1.0 (1.0, 1.0)*	0.019[a]
2 h rest NRS	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.530[a]
6 h rest NRS	1.0 (1.0, 2.3)	1.0 (1.0, 2.0)	0.633[a]
12 h rest NRS	1.0 (0.0, 2.0)	1.0 (0.8, 1.0)	0.530[a]
24 h rest NRS	1.0 (0.0, 1.3)	1.0 (0.0, 1.0)	0.430[a]
48 h rest NRS	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.923[a]
0.5 h cough NRS	2.5 (1.0, 3.0)	1.0 (1.0, 2.0)**	0.003[a]
2 h cough NRS	2.0 (1.8, 3.0)	2.0 (1.0, 3.0)	0.584[a]
6 h cough NRS	2.5 (1.0, 4.0)	2.0 (1.8, 3.0)	0.813[a]
12 h cough NRS	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.836[a]
24 h cough NRS	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.820[a]
48 h cough NRS	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.933[a]

Notes: Date are presented median (interquartile range). *P <0.05; **P<0.01. Statistical tests for *P*-value calculation: [a]Wilcoxon rank-sum test.
Abbreviations: Group M, morphine group; Group O, oliceridine group; NRS, Numerical Rating Scale (0 = no pain to 10 = worst pain).

Comparative SpO_2 analysis after postoperative loading doses revealed differential oxygenation patterns. Group O maintained superior median SpO_2 at 5 min (100 [96, 100] vs 97 [90, 100]; $P = 0.003$) and 10 min (100 [98, 100] vs 98 [92, 100]; $P = 0.033$), with intergroup equivalence emerging by 15 min (100 [98, 100] vs 98 [93, 100]; $P = 0.330$) and 30 min (100 [99, 100] vs 99 [99, 100]; $P = 0.344$]) post-administration (Figure 2).

After loading dose administration, group M displayed a transient increase in HR from baseline at 5 min, which subsequently trended downward by 10 min. In contrast, oliceridine maintained hemodynamic stability with no clinically meaningful HR increases related to baseline throughout the observation period, with statistically significant reductions in HR observed at 10, 15, and 30 min (all $P < 0.05$). Both groups maintained hemodynamic homeostasis, as evidenced by the absence of significant NIBP deviations from baseline values (all $P > 0.05$; Figure 3).

Comparative analysis of postoperative recovery metrics revealed significant intergroup distinctions in gastrointestinal function. Group O demonstrated a significantly earlier return of bowel function (24.53 ± 7.14 vs 32.70 ± 8.88 h; $P < 0.001$) and superior 24-hour postoperative QoR-15 score performance (125.27 ± 10.11 vs 119.67 ± 8.49; $P = 0.024$) compared with

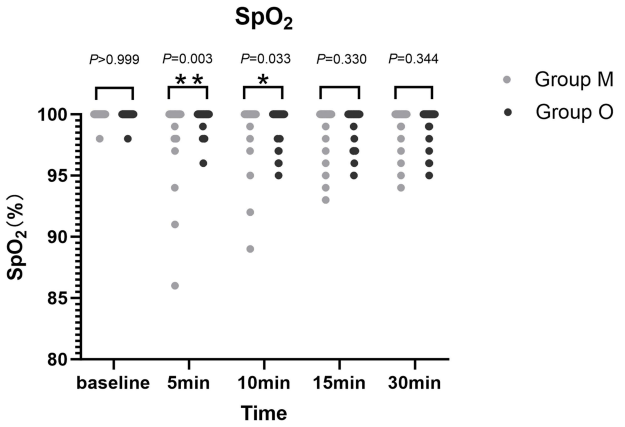

Figure 2 SpO_2 at specified intervals following intravenous administration of analgesic loading dose. Group O maintained higher SpO_2 at 5 min and 10 min, with intergroup differences becoming non-significant at 15 min and 30 min. SpO_2: peripheral capillary oxygen saturation.Statistical tests for *P*-value calculation: Mann–Whitney *U*-test. **P* <0.05; ***P* <0.01.

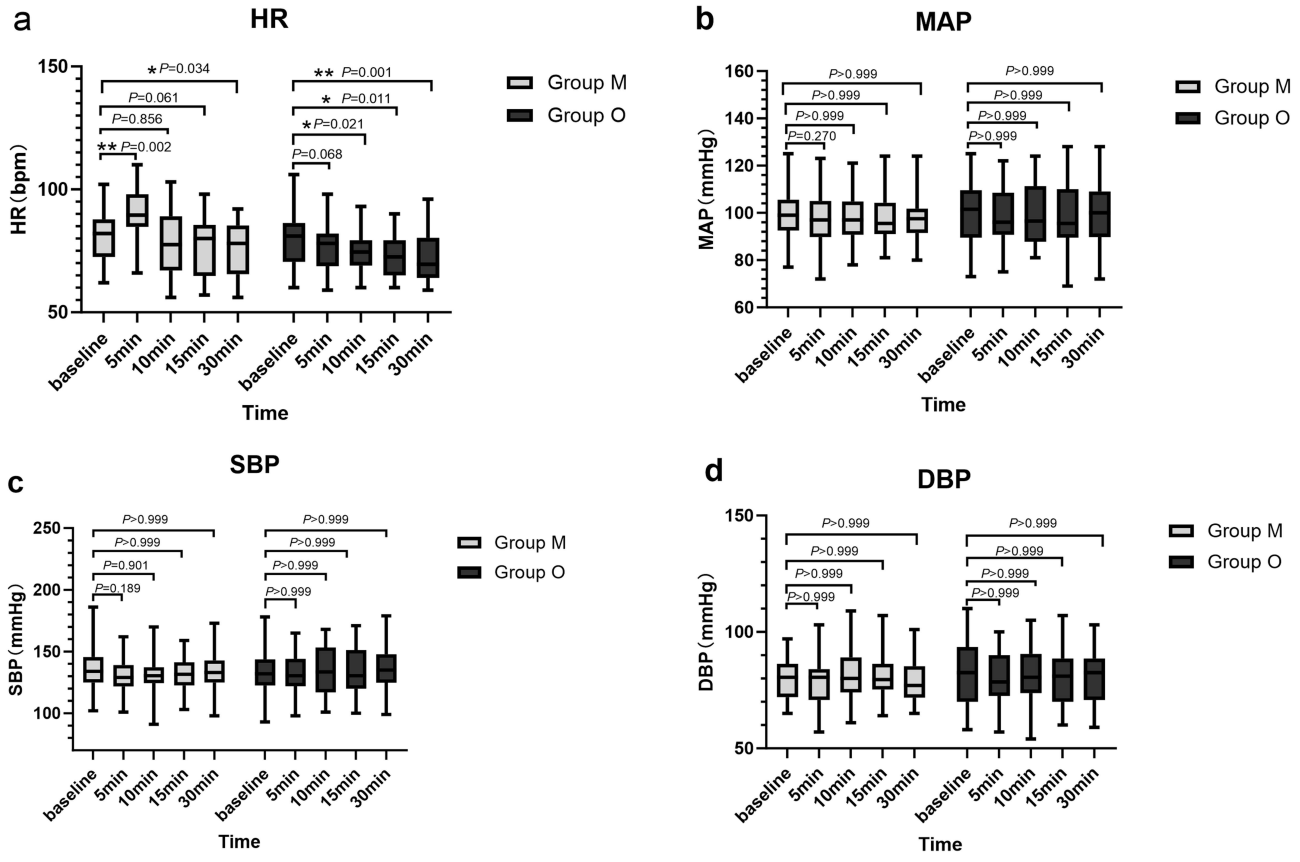

Figure 3 Hemodynamic comparisons between Group M and Group O. (**a**) Heart Rate (HR): Group M showed transient HR elevation at 5 min (vs baseline), declining by 10 min. Oliceridine maintained hemodynamic stability with clinically insignificant HR fluctuations and demonstrated statistically lower HR at 10, 15, and 30 min (*P*<0.05). (**b–d**) All hemodynamic parameters (including HR, MAP, SBP, DBP) were analyzed using Greenhouse-Geisser corrected repeated measures ANOVA for within-group time-point comparisons, with *P*-values explicitly annotated in the figure Intergroup baseline differences were confirmed non-significant by independent samples *t*-test (all *P*>0.05). **P* <0.05; ***P* <0.01.
Abbreviations: MAP, Mean Arterial Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

group M. Both groups demonstrated comparable postoperative analgesic utilization patterns, with no significant differences in PCIA activation counts within 48 h (3.00 [2.00, 7.00] vs 3.00 [2.00, 7.25]; $P = 0.470$) or analgesic rescue requirements (13.3% vs 13.3%; $P > 0.999$). No significant intergroup differences were observed in ambulation (20.07 ± 6.72 vs 21.30 ± 4.02 h; $P = 0.392$) and hospitalization duration (7 [6,7] vs 7 [6,7] days; $P = 0.719$) (Table 3).

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Table 3 Postoperative Outcomes

	Group M (n=30)	Group O (n=30)	*P* value
First Postoperative Flatus, h	32.70±8.88	24.53±7.14**	<0.001[a]
First Postoperative Ambulation, h	21.30±4.02	20.07±6.72	0.392[a]
Counts of PCIA activation, times	3.00 (2.00,7.25)	3.00 (2.00,7.00)	0.470[b]
Postoperative analgesic remedy, n (%)	4(13.3%)	4(13.3%)	>0.999[c]
Postoperative tramadol Consumption, mg	61.50±2.73	61.00±1.47	0.347[a]
QoR-15 at 24h postoperatively, points	119.67±8.49	125.27±10.11*	0.024[a]
Length of hospital stay, days	7(6,7)	7(6,7)	0.719[b]

Notes: Date are presented as mean ± SD, median (interquartile range), or number (percentage). *P <0.05; **P <0.01. Statistical tests for P-value calculation: [a]independent samples t-test, [b]Mann–Whitney U test, [c]Chi-square test with continuity correction.
Abbreviations: Group M, morphine 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

	Group M (n=30)	Group O (n=30)	*P* value
Post-operative adverse events, n (%)	25(83.3%)	15(50.0%)**	0.006[a]
Nausea/Vomiting, n (%)	22(73.3%)	10(33.3%)**	0.002[a]
Constipation, n (%)	16(53.3%)	6(20.0%)**	0.007[a]
Pruritus, n (%)	3(10.0%)	0(0.0%)	0.236[b]
Dizziness, n (%)	3(10.0%)	0(0.0%)	0.236[b]
Chest tightness, n (%)	1(3.3%)	1(3.3%)	>0.999[b]
Blurred vision, n (%)	2(6.7%)	0(0.0%)	0.472[b]
Somnolence, n (%)	3(10.0%)	2(6.7%)	>0.999[b]

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

Safety Outcomes

Group O demonstrated significantly lower incidence rates of postoperative nausea/vomiting (33.3% vs 73.3%; $P = 0.002$) and constipation (20.0% vs 53.3%; $P = 0.007$) compared with group M. Numerically higher rates of ORAEs were observed in group M, including pruritus (10.0% vs 0.0%; $P = 0.236$), dizziness (10.0% vs 0.0%; $P = 0.236$), blurred vision (6.7% vs 0.0%; $P > 0.999$), and somnolence (10.0% vs 6.7%; $P > 0.999$); however, these differences failed to achieve statistical significance. Strikingly, group O exhibited a significantly lower overall adverse event rate compared with group M (50% vs 83.3%; $P = 0.002$) (Table 4).

Discussion

The results of this study revealed that oliceridine provides postoperative analgesic efficacy comparable to morphine while demonstrating a more favorable safety profile, with reduced ORAEs incidence, including postoperative nausea/vomiting, respiratory depression, and constipation. These results indicate the potential application of this approach in clinical settings where improved recovery protocols require effective analgesia with improved tolerability.

Our findings demonstrate superior early postoperative analgesia with oliceridine compared with morphine, as evidenced by significantly improved resting and cough NRS scores at 30 min postoperatively. This phenomenon originates from oliceridine's unique G-protein biased μ-opioid receptor activation profile. Mechanistic studies reveal preferential coupling of oliceridine to inhibitory G-protein subunits accelerates nociceptive signal blockade while minimizing β-arrestin recruitment, which is a molecular signature enabling faster pain signal transduction inhibition than morphine.[22] Pharmacodynamic modeling confirmed that oliceridine achieves peak analgesic efficacy within 5–15 min post-IV injection, contrasting with morphine's 15–30 min onset period (notable interindividual variability).[23] Despite oliceridine's shorter elimination half-life (1.6–2.7 h vs morphine's 2.4–6.7 h),[24] equivalent analgesic

maintenance (2–48 h) emerged through PCIA-driven pharmacokinetic compensation. Both agents sustained plasma concentrations above minimum effective analgesic thresholds during steady-state infusion. The trial data exhibited no statistically significant differences in counts of PCIA activation, rescue analgesia requirements, or tramadol consumption between the groups, confirming that oliceridine's PCIA efficacy matches morphine's performance.

Previous investigations have identified that opioid-induced histamine release mediates transient cardiovascular activation characterized by tachycardia and hypertension.[25] In our study, group M exhibited an increase in HR from baseline at 5 min postloading dose, followed by a declining trend at 30 min. This result is consistent with previous research evidence. In contrast, oliceridine administration demonstrated no significant HR elevation compared with baseline at any measured interval, with statistically significant reductions observed at 10-, 15-, and 30-min time points (all $P < 0.05$). This phenomenon may be related to oliceridine's rapid analgesic onset (5–15 min vs morphine's 15–30 min),[23] where prompt pain relief-induced parasympathetic activation potentially offsets histamine-mediated tachycardia, and/or its β-arrestin-biased signaling that prevents histamine exocytosis. Notably, neither group demonstrated significant fluctuations in blood pressure from baseline, although NIBP monitoring limitations in temporal resolution may have obscured transient hemodynamic changes. These results collectively indicate oliceridine's superior hemodynamic stability profile compared with conventional opioids.

The most clinically significant findings are derived from the comparative adverse effect profiles. Compared with morphine, oliceridine demonstrated a reduction in postoperative nausea/vomiting incidence and lower constipation rates, consistent with previous results.[26–28] Moreover, a significantly shorter time to the first postoperative flatus in group O indicates accelerated gastrointestinal recovery, with reduced β-arrestin recruitment in enteric neurons that potentially explain both the lower gastrointestinal complication risk and faster functional restoration.[29] Our respiratory safety data reinforce oliceridine's pharmacological superiority, with sustained higher SpO_2 levels postloading dose being congruent with mechanistic evidence of reduced respiratory depression through selective G-protein coupling.[16,30,31] This finding helped improve respiratory safety profiles compared with morphine. These favorable pharmacodynamic properties collectively indicate accelerated postoperative recovery pathways.

Furthermore, our analysis revealed that group O demonstrated significantly higher QoR-15 scores at 24 h postoperatively compared with group M (125.27 ± 10.11 vs 119.67 ± 8.49, $P = 0.024$). This observation may be mechanistically associated with the reduced incidence of adverse events and accelerated gastrointestinal functional recovery in group O. However, the collective results provide further evidence supporting the theory that oliceridine improves postoperative recovery through its favorable safety profile and prokinetic effects.

This study has several limitations that warrant consideration. The single-center design and exclusive female patient population limit the generalizability to other surgical contexts and demographic groups. Our 48-h observation window precludes the assessment of chronic pain outcomes, which is an important consideration given the emerging associations between acute opioid exposure and persistent postsurgical pain. Furthermore, intraoperative anesthetic consumption was neither recorded nor compared as a baseline between groups. Future research directions are recommended to include multicenter trials that compare oliceridine with other opioids, such as sufentanil, in diverse surgical populations. Longitudinal studies that assess long-term outcomes, including opioid-induced hyperalgesia and persistent pain development, could further clarify oliceridine's role in modern opioid stewardship programs.

Conclusion

Oliceridine, which is a novel μ-opioid receptor agonist with G-protein biased signaling properties, demonstrated non-inferior analgesic efficacy to morphine in postoperative pain management while exhibiting superior safety profiles, as evidenced by significantly reduced opioid-induced respiratory depression and postoperative nausea/vomiting incidence, with minimal hemodynamic compromise. This unique pharmacological profile positions it as an optimal candidate for improved recovery protocols that require meticulous equilibrium between analgesia optimization and adverse event mitigation.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author Xia Ju (Email: alcon2006@126.com) upon reasonable request.

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Disclosure

All authors declare no financial or non-financial conflicts of interest that could influence the study outcomes, including the verifiable absence of economic associations with pharmaceutical entities.

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