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Original Article

Effects of oliceridine-based patient-controlled intravenous administration on postoperative pain and hemodynamic stability in elderly patients undergoing laparoscopic surgery for colorectal cancer

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Abstract: The dose-effect relationship and hemodynamic effects of oliceridine in elderly patients undergoing laparoscopic surgery remain unclear. This study evaluated the effects of different doses of oliceridine administered via patient-controlled intravenous analgesia (PCIA) on postoperative pain management in older adults with colorectal cancer. Patients were divided into three groups according to the analgesic regimen: a control group (Group C, fentanyl PCIA), a low-dose oliceridine group (Group O1), and a high-dose oliceridine group (Group O2), each comprising 50 patients. Outcomes included resting and movement numeric rating scale (NRS) scores, incidence of moderate-to-severe pain, Ramsay sedation scores, Quality of Recovery-15 (QoR-15) scores, patient satisfaction, inflammatory cytokine levels, hemodynamic and respiratory parameters, and adverse reactions. The total opioid load was similar across the three groups. Group O2 showed consistently lower resting and movement NRS scores at all observation time points (all $P<0.001$). It also had the lowest frequency of moderate-to-severe pain within the first 48 hours after surgery ($P<0.05$). In addition, patients in the O2 group achieved earlier first ambulation and had a shorter length of hospital stay than the other groups ($P<0.05$). Group O2 also showed a higher QoR-15 score, indicating better postoperative recovery quality ($P<0.001$), along with higher analgesic satisfaction ($P=0.001$). Inflammatory cytokine levels decreased dose-dependently ($P<0.001$). Hemodynamic parameters were more stable, and respiratory rate and saturation (SpO_2) improved more significantly in Group O2 ($P<0.05$). The incidence of adverse reactions was comparable among the three groups of people ($P>0.05$). The number of remedial analgesia administrations within 24 hours postoperatively (0.4±0.2 times) and total flurbiprofen axetil consumption (25.0±12.5 mg) were significantly lower in Group O2 than in Groups O1 and C ($P<0.05$). High-dose Oliceridine PCIA provided better analgesic effects for elderly Laparoscopic Colorectal Cancer Patients after surgery, effectively reduced inflammatory response, and maintained stable Hemodynamic and Respiratory Function.

Keywords: Intravenous patient-controlled analgesia, oliceridine, elderly patients, laparoscopic colorectal cancer surgery, postoperative pain

Introduction

Colorectal cancer is a common digestive tract malignancy in elderly patients. Laparoscopic surgery has become increasingly popular due to its minimally invasive nature, including smaller incisions and faster postoperative recovery [1]. Postoperative pain is a crucial factor affecting early functional rehabilitation in elderly patients [2]. Elderly patients often present with multiple comorbidities and impaired liver and kidney function, resulting in reduced drug metabolism capacity. In addition, increased opioid sensitivity in this population predisposes them to adverse effects such as respiratory depression, cognitive dysfunction, nausea, and vomiting [1-5]. Therefore, optimizing perioperative analgesic strategies in elderly patients with colorectal cancer is essential to ensure treatment safety while achieving adequate pain control.

Patient-controlled intravenous analgesia (PCIA) is currently the most commonly used modality

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for postoperative analgesia. Traditional regimens primarily rely on μ-receptor agonists, such as fentanyl and sufentanil [6, 7]. Although these drugs provide effective analgesic effects, excessive -receptor activation is associated with adverse reactions such as respiratory depression, suppression of gastrointestinal motility, and urinary retention. Elderly patients are more prone to these complications. In recent years, increasing attention has been paid to the novel opioid Oliceridine owing to its distinctive pharmacodynamic profile. As a G protein-biased μ-opioid receptor agonist, oliceridine exerts potent analgesic effects through preferential activation of the G protein signaling pathway, while its low activity at the β-arrestin pathway mitigates μ-opioid receptor-related respiratory depression and gastrointestinal adverse reactions [8]. Studies have shown that oliceridine provides stable analgesia in abdominal surgery [9] and burn surgery [10], with minor impact on respiratory and cardiovascular function.

In this study, we evaluated the perioperative efficacy of two dosage regimens of oliceridine administered via PCIA and compared them with a standard fentanyl-based PCIA protocol in elderly patients undergoing laparoscopic colorectal cancer surgery. The effects of oliceridine on pain control, circulatory and respiratory stability, and overall rehabilitation in elderly patients were systematically evaluated.

Materials and methods

Study subjects

This study was approved by the Ethics Committee of The First Affiliated Hospital of Nankai University. Clinical data were retrospectively collected from 150 elderly patients who underwent elective laparoscopic surgery for colorectal cancer at our hospital between June 2024 and December 2025. According to the analgesic regimen, patients were divided into three groups: a control group (Group C), a low-dose oliceridine group (Group O1), and a high-dose oliceridine group (Group O2), with 50 patients in each group.

The sample size was determined by the availability of clinical data within the predetermined enrollment window (June 2024 to December 2025). A post hoc sensitivity analysis performed using G*Power software (version 3.1.9.7) indicated that the achieved sample size (50 patients per group) provided 90% power to detect a clinically meaningful difference in the primary outcome measure (resting NRS score at 24 hours postoperatively) at a two-tailed significance level of 0.05.

Inclusion criteria: (1) Age between 65 and 80 years; (2) American Society of Anesthesiologists (ASA) physical status classification I-III; (3) Body mass index (BMI) of 18.5-24.9 kg/m^2; (4) Scheduled to undergo elective lower abdominal colorectal cancer surgery under general anesthesia; (5) Received postoperative PCIA.

Exclusion criteria: (1) Significant hepatic or renal dysfunction, defined as any of the following: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN), or total bilirubin >1.5 × ULN, or Child-Pugh grade ≥B; estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (calculated by the CKD-EPI formula), or requirement for renal replacement therapy (e.g., dialysis); (2) Metabolic equivalents (METs) <4; (3) History of anesthetic or sedative drug abuse; (4) Known hypersensitivity to study-related drugs; (5) Emergency reoperation; (6) Requirement for postoperative intensive care unit (ICU) admission; (7) Deemed ineligible for inclusion by the investigators based on clinical judgment.

A dynamic titration protocol for postoperative PCIA was adopted according to institutional guidelines. When the resting NRS score was ≥4 or the movement-evoked NRS score was ≥5, the patient-controlled analgesia (PCA) bolus dose was increased by 10%-20% according to a predefined escalation algorithm until the adequate analgesia (NRS<3) was achieved. Dose adjustments were performed no more frequently than every 30 minutes after the last bolus. A maximum cumulative dose was predefined, with escalation not exceeding 20% of the baseline regimen. Dose reduction or discontinuation was mandated in cases of adverse reactions such as persistent severe pain (NRS≥ 7), excessive sedation (Ramsay score >4), or respiratory depression (RR<8 breaths/min). The primary objective of this titration strategy was to maintain equivalent analgesic levels (target NRS<3) across the three groups within 48 hours postoperatively, enabling comparison of cumulative opioid requirements under equivalent analgesic conditions.

Based on a preliminary experiment in 30 patients, the minimum effective bolus dose required to achieve NRS<3 were estimated as fentanyl 2 mL/bolus, oliceridine 0.2 mg/bolus, and 0.35 mg/bolus for low- and high-dose regimens, respectively. The formal PCIA settings were as follows: Group C (fentanyl): loading dose 4 ml, PCA bolus dose 2 ml (containing fentanyl 0.01 mg); Group O1 (low-dose Oliceridine): loading dose 1.5 mg, PCA bolus dose 0.2 mg; Group O2 (high-dose Oliceridine): loading dose 1.5 mg, PCA bolus dose 0.35 mg. Different loading dose strategies were adopted to achieve equivalent initial analgesic coverage across groups. In Group C, fentanyl 200 μg (4 mL, 50 μg/mL) was administered as the loading dose, consistent with routine clinical practice and pilot study. In Groups O1/O2, oliceridine 1.5 mg was administered as the loading dose, designed to approximate the onset of analgesia observed in the fentanyl group, based on an estimated oliceridine-to-fentanyl potency ratio of approximately 7.5:1 derived from the pilot study. Although absolute loading doses differed between groups, the intent was to ensure rapid achievement of the target analgesic level at the initiation of PCA, thereby eliminating inter-group differences in baseline pain intensity.

If inadequate analgesia occurred during treatment, flurbiprofen axetil 50 mg was administered intravenously as rescue analgesia and was included in the calculation of total postoperative opioid consumption. Rescue analgesia was defined as administration when resting NRS score was ≥4 and was confirmed to be non-neuropathic. The standard dose was 50 mg per administration via slow intravenous injection over at least 1 minute. In patients weighing <50 kg or aged >75 years, the dose was reduced to 25 mg per administration. Administration frequency was limited to a maximum of three doses within 24 hours to reduce the risk of NSAID-related adverse effects. Once severe nausea or vomiting was developed, antiemetic therapy, including 5-HT3 receptor antagonists, was administered as required.

Standardized calculation of opioid consumption

Due to the significant difference in pharmacological potency between fentanyl and oliceridine, direct comparison of cumulative doses in milligrams (mg) is no appropriate. Therefore, opioid consumption was standardized using oral morphine milligram equivalents (MME) to enable comparison of equivalent analgesic exposure across groups. Total opioid consumption was calculated as follows: Total MME (mg) = [Fentanyl dose * CF_fent] + [Oliceridine dose * CF_olic], where CF denotes conversion factor.

Fentanyl Conversion Factor (CF_fent): Our preliminary study and commonly accepted equianalgesic standards indicated that the equianalgesic conversion factor for intravenous fentanyl to oral morphine was 100 (i.e., 1 mg of intravenous fentanyl was equivalent to 100 mg of oral MME).

Oliceridine Conversion Factor (CF_olic): As oliceridine is a novel G-protein-biased μ-opioid receptor agonist, it is not currently included in the standard MME conversion table, making direct potency conversion challenging. Therefore, the equianalgesic relationship between oliceridine and fentanyl was estimated based on a preliminary dose-finding experiment, supplemented by published clinical evidence.

First, pharmacological data suggest that 1 mg of intravenous oliceridine is approximately equivalent to 5 mg of intravenous morphine. Second, the APOLLO-2 Phase III clinical trial [11] demonstrated that patient-controlled doses of 0.35 mg and 0.5 mg of oliceridine provide analgesia comparable to 1 mg morphine. Collectively, these data support an estimated oliceridine-to-morphine equianalgesic ratio of approximately 1: (2.0-2.9).

By integrating the clinically accepted MME conversion factor for fentanyl (1 mg of intravenous fentanyl ≈ 100 mg of oral MME) and the established potency ratio between intravenous morphine and fentanyl (≈ 100:1), the equianalgesic ratio of oliceridine to fentanyl was estimated to be approximately 7.5:1. Accordingly, the MME conversion factor for oliceridine was set at 13.33. Notably, the calculated MME values based on the estimated CF (13.3) were used solely for within-study comparisons of opioid consumption and should not be generalized to other clinical settings or populations.

Study methods

Upon arrival in the operating room, a peripheral intravenous cannula was established in each

patient, and normal saline infusion was initiated. Regular monitoring of body temperature, heart rate (HR), blood pressure (BP), and peripheral oxygen saturation (SpO_2) was commenced. A bispectral index (BIS) monitor was used to continuously measure the depth of general anesthesia. General anesthesia was induced via rapid intravenous injection of the following agent: midazolam (0.02 mg/kg; Jiangsu Nhwa Pharmaceutical Co., Ltd., China), fentanyl (2 μg/kg; Jiangsu Nhwa Pharmaceutical Co., Ltd., China), etomidate (0.3 mg/kg; Yangtze River Pharmaceutical Group Co., Ltd., China), and cisatracurium besilate (0.15 mg/kg; Shanghai Hengrui Medicine Co., Ltd., China). Orotracheal intubation was performed using video laryngoscopy after 2-3 minutes of mask ventilation.

During surgery, airway pressure was kept below 30 cm H_2O, and end-tidal carbon dioxide ($PETCO_2$) was controlled within 35-45 mmHg. Anesthesia was sustained using a target-controlled infusion (TCI) technique with continuous intravenous infusion of propofol and remifentanil, supplemented by intermittent boluses of cisatracurium besilate. The infusion rates of propofol (Jiangsu Nhwa Pharmaceutical Co., Ltd., China) and remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., China) were adjusted to maintain BIS between 40 and 60. Routine perioperative temperature preservation was performed to maintain nasopharyngeal temperature above 36°C. At the end of surgery, all anesthetic drugs were discontinued. Muscle relaxants were discontinued approximately 30 minutes before the completion of the operation. Local infiltration anesthesia was administered with 20 ml of 0.5% ropivacaine hydrochloride before abdominal closure. Tracheal extubation was performed when patients were conscious, responsive to verbal commands, and demonstrated intact protective airway reflexes (pharyngeal, swallowing, and cough reflexes), with restoration of normal tidal volume and minute ventilation.

Patients were transferred to the post-anesthesia care unit (PACU) upon achieving a Steward recovery score >4 points. In the PACU, supplemental oxygen was delivered via nasal cannula, and continuous monitoring of electrocardiogram, oxygen saturation, and blood pressure was maintained. Patients were returned to the wards after a minimal observation period of 30 minutes, during which the Steward score consistently remained >PCIA protocol: PCIA was delivered using a patient-controlled analgesia pump, with identical pump settings to ensure comparability between groups: background infusion rate of 4 mL/h, lockout interval of 15 minutes, and a maximum dose limit of 10 boluses every 4 hours.

Observation indicators

(1) Baseline demographic characteristics: Baseline data were collected for all patients, including age, sex, and educational level; (2) Postoperative pain assessment: Perioperative pian was evaluated using the Numeric Rating Scale (NRS) [12]. Resting NRS (NRS-R) scores were recorded at extubation (T0) and at 1, 2, 4, 8, 12, 24, and 48 hours postoperatively. Movement NRS (NRS-M) scores were assessed at 4, 8, 12, 24, and 48 hours after surgery. Episodes of moderate-to-severe pain were documented, defined as any NRS score ≥4 within the first 48 postoperative hours; (3) Sedation and sleep-related outcomes: Sedation status was evaluated using the Ramsay Sedation Scale [13] at 1, 2, 4, 8, 12, 24, and 48 hours postoperatively (scores range from 1 to 6, with higher scores indicating deeper sedation); (4) Quality of recovery and patient satisfaction: Postoperative recovery quality was assessed using the Quality of Recovery-15 (QoR-15) questionnaire [14], delivered preoperatively and on postoperative days 1 and 2 (range 0-150, with higher scores indicating better recovery). Analgesic satisfaction was evaluated at 48 hours postoperatively employing a 5-point Likert scale (very dissatisfied, dissatisfied, neutral, satisfied, and very satisfied); (5) Inflammatory and tissue injury biomarkers: Peripheral venous blood samples were collected preoperatively and at 24 and 72 hours postoperatively, to determine serum levels of interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and matrix metalloproteinase (MMP); (6) Hemodynamic and respiratory parameters: Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), and pulse oxygen saturation (SpO_2) were recorded preoperatively, and at 24 and 48 hours postoperatively; (7) Perioperative clinical outcomes: Preoperative data were collected, including intraoperative doses of propofol and remifentanil, fluid infusion volume, intraopera-

Table 1. Baseline characteristics of the three groups

Indicator	Group C (n=50)	Group O1 (n=50)	Group O2 (n=50)	χ^2/F	*P*
Gender (cases)				1.784	0.410
Male	30	32	31		
Woman	20	18	19		
Age (years)	72.31±8.67	73.48±7.25	73.22±7.62	0.783	0.572
Years of education (years)	12.28±2.26	12.81±2.37	12.64±2.23	0.824	0.518

Note: Group C: Fentanyl group; Group O1: Low-dose oliceridine group; Group O2: High-dose oliceridine group.

tive blood loss, urine output, surgical duration, anesthesia duration, time to postoperative mobilization, length of postoperative hospital stay, and incidence of adverse events (e.g., nausea, emesis, dizziness, respiratory depression, hypoxemia); (8) Patient-controlled analgesia (PCA) parameters: Using the built-in data recording function of the electronic PCA pump, PCA-related parameters over the first 48 postoperative hours were extracted, including total number of PCA demand attempts, number of successful deliveries (i.e., effective boluses delivered after lockout confirmation), and total administered bolus dose in each group.

Statistical analysis

Statistical analyses were conducted using SPSS 26.0 software. Data distribution was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation (sd) and were compared between groups using independent-samples t-tests. Non-normally distributed continuous variables were reported as median (interquartile range) and were analyzed using the Mann-Whitney U test. Categorical variables were summarized as frequency and percentage [n (%)] and were compared using the χ^2 test or Fisher's exact test, as appropriate. For repeated measurements over time (e.g., NRS scores, Ramsay sedation scores, and inflammatory cytokines), a two-way repeated-measures ANOVA was employed to assess the effects of the intervention over time. Sphericity was evaluated using Mauchly's test, and when the assumption of sphericity was violated ($P<0.05$), the Greenhouse-Geisser correction was applied. When a significant main effect was observed, post-hoc pairwise comparisons were performed using the Bonferroni correction. A two-tailed $P<0.05$ was considered statistically significant.

Results

General characteristics of patients across groups

The baseline characteristics of the study subjects are shown in **Table 1**. There were no significant differences in sex distribution, age, or years of education among the three groups (all $P>0.05$), indicating that the three groups were comparable at baseline.

NRS scores in different groups at each time point

Two-way ANOVA was performed to analyze NRS-R. Mauchly's test revealed a violation of the sphericity assumption ($P<0.001$), and the Greenhouse - Geisser correction was applied ($\varepsilon=0.73$). The analysis revealed a significant group × time interaction effect ($F(9.5, 698.3)=4.21$, $P<0.001$), as well as significant main effects of group ($F(2, 147)=15.25$, $P<0.001$) and time ($F(4.8, 349.1)=26.34$, $P<0.001$).

For NRS-M, two-way repeated-measures similarly demonstrated a violation of sphericity ($P<0.001$, $\varepsilon=0.69$). A significant interaction effect was observed ($F(5.5, 404.3)=3.85$, $P=0.001$), together with significant main effects of group ($F(2, 147)=17.23$, $P<0.001$) and time ($F(2.8, 202.1)=22.14$, $P<0.001$).

Subsequent pairwise post-hoc comparisons with Bonferroni correction indicated that the O2 group consistently exhibited significantly lower NRS-R scores compared with both the C and O1 group across all postoperative time points (T0-T7) ($P<0.05$). For NRS-M scores, the O2 group showed significantly lower scores than the C and O1 groups at time points T3-T7 ($P<0.05$). Details are presented in **Tables 2**, **3**. Although there was a general decreasing trend in pain intensity over time in all groups, Group

Table 2. Comparison of NRS-R scores among groups at different time points

Group	NRS-R							
	T0	T1	T2	T3	T4	T5	T6	T7
Group C (n=50)	4.26±1.13	4.56±1.26	4.34±1.36	4.06±1.29	3.72±1.32	3.42±1.28	2.99±1.13	2.30±1.00
Group O1 (n=50)	3.64±1.05	3.85±1.17	3.77±1.24	3.42±1.13	3.15±1.25	2.84±1.16	2.34±1.03	1.80±0.90
Group O2 (n=50)	3.12±0.96	3.34±1.02	3.20±1.16	2.98±1.06	2.68±1.14	2.39±1.06	1.86±0.98	1.40±0.80

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. NRS-R: Numeric Rating Scale-Rest. T0: Immediately after extubation; T1: 1 h postoperatively; T2: 2 h postoperatively; T3: 4 h postoperatively; T4: 8 h postoperatively; T5: 12 h postoperatively; T6: 24 h postoperatively; T7: 48 h postoperatively.

Table 3. Comparison of NRS-M scores among groups at different time points

Group	NRS-M				
	T3	T4	T5	T6	T7
Group C (n=50)	5.84±1.49	5.52±1.59	5.26±1.46	4.69±1.33	3.80±1.20
Group O1 (n=50)	5.09±1.35	4.76±1.43	4.34±1.32	3.82±1.26	3.10±1.10
Group O2 (n=50)	4.47±1.22	4.03±1.37	3.77±1.29	3.18±1.15	2.50±1.00

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. NRS-M: Numeric Rating Scale-Motion. T3: 4 h postoperatively; T4: 8 h postoperatively; T5: 12 h postoperatively; T6: 24 h postoperatively; T7: 48 h postoperatively.

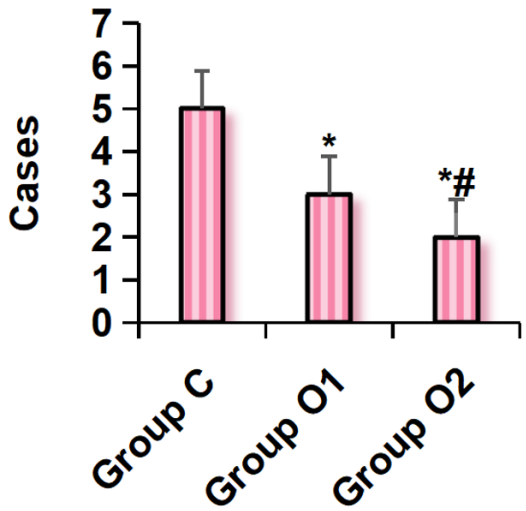

Figure 1. Comparison of incidence of moderate-to-severe pain within 48 hours postoperatively among groups. Note: *P<0.05, compared with Group C; #P<0.05, compared with Group O1. Group C: Fentanyl group, n=50; Group O1: Low-dose Oliceridine group, n=50; Group O2: High-dose Oliceridine group, n=50.

O2 maintained the lowest pain intensity throughout the observation period. The analgesic advantage of the O2 group was more pronounced for movement-evoked pain during the early postoperative period (T3-T6) (P<0.001).

Figure 1 shows the incident of moderate-to-severe pain (NRS≥4) within the first 48 hours after surgery. The highest incidence was observed in Group C (5 cases), followed by Group O1 (3 cases) and Group O2 (2 cases), with significant differences among groups (P<0.05).

Perioperative outcomes across groups

Figure 2 presents a comparative overview of multiple perioperative parameters among the three study groups. No significant differences were observed in intravenous fluid volume, intraoperative blood loss, urine output, surgical duration, anesthesia duration, or extent of surgical scope among the groups (all P>0.05), indicating comparability of perioperative management.

However, time to first postoperative ambulation was notably shorter in Group O2 compared with the other two groups (P<0.05). Additionally, postoperative length of hospital stay was significantly reduced in Group O2 relative to the other two groups (P<0.05).

Comparison of opioid consumption between groups

Table 4 presents the comparison of opioid consumption among the three groups. A significant difference was observed in the raw total consumption of oliceridine between the two oliceridine groups (Group O1: 3.80±0.95 mg

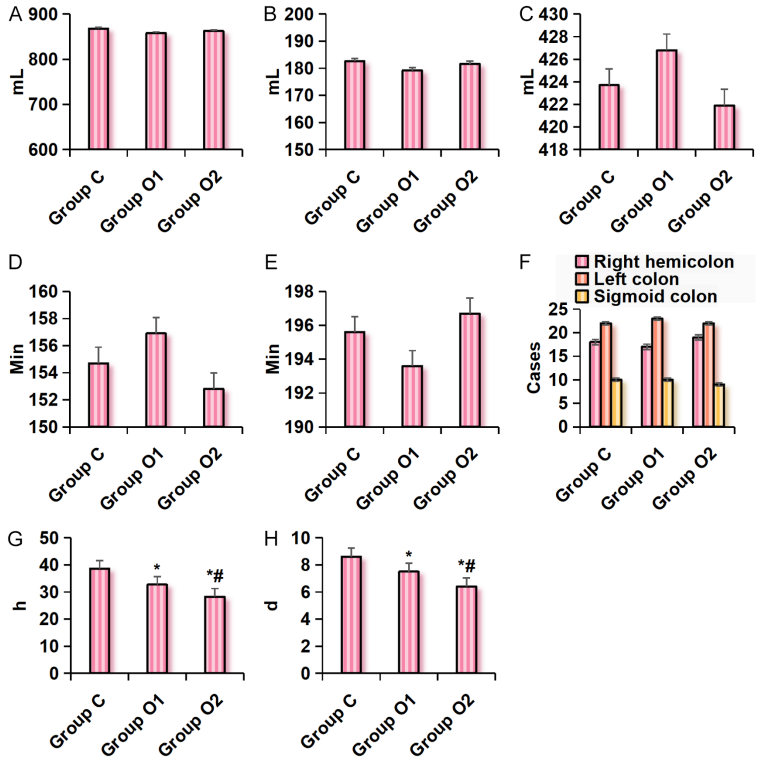

Figure 2. Comparison of perioperative outcomes among groups. A. Fluid volume; B. Blood loss; C. Urine output; D. Duration of surgery time; E. Duration of anesthesia; F. Surgical scope; G. Time to first postoperative ambulation; H. Postoperative hospital stays. Notes: *P<0.05, compared with Group C; #P<0.05, compared with Group O1. Group C: Fentanyl group, n=50; Group O1: Low-dose Oliceridine group, n=50; Group O2: High-dose Oliceridine group, n=50.

Table 4. Comparison of opioid consumption among groups

Group	Total fentanyl consumption (mg)	Total Oliceridine consumption (mg)	Total opioid consumption (MME, mg)
Group C (n=50)	0.45±0.12	-	45.0±12.0
Group O1 (n=50)	-	3.80±0.95	50.5±12.6
Group O2 (n=50)	-	3.20±0.80	42.6±10.6
t/F	-	3.416	5.926
P	-	0.001	0.003

vs. Group O2: 3.20±0.80 mg; P=0.001), indicating that the high-dose regimen was associated with a lower drug requirement. However, no significant difference was found in total opioid consumption after conversion to oral MME among the three groups (P=0.485). The total MME for Group C, Group O1, and Group O2 were 45.0±12.0 mg, 48.5±12.6 mg, and 44.6±10.6 mg, respectively.

Overall, after standardization using MME conversion, opioid exposure was comparable across the three regimens, suggesting that the equianalgesic titration protocol effectively achieved comparable analgesic burden among groups.

Comparison of PCA pump usage parameters among groups

PCA pump usage data within 48 hours postoperatively are summarized in **Table 5**. The total number of PCA demands was significantly lower in Group O2 (9.6±3.8) compared with Group O1 group (14.8±4.6) and Group C (18.5±5.2) (P< 0.01). Similarly, the number of effective PCA deliveries was significantly lower in Group O2 (8.2±3.1 per 48 h) than Group O1 (12.5±4.0 per 48 h, P<0.01) and Group C (15.8±4.5 per 48 h, P<0.001). The total number of actual drug administrations showed a similar trend across groups.

Regarding bolus dose per administration, the planned dose per effective compression was 0.35 mg in Group O2, higher than 0.20 mg in Group O1. These findings indicate that patients in the high-dose oliceridine group achieved adequate analgesia with fewer PCA demands and successful boluses, suggesting a more sustained analgesic effect per administration.

Ramsay sedation scores across postoperative time points

Table 6 presents Ramsay sedation scores across the three groups at different postoperative time points. Two-way repeated-measures ANOVA revealed a significant group × time interaction effect (F (8.2, 602.7)=2.94, P=0.003), as well as significant main effects of group (F (2, 147)=5.72, P=0.004) and time (F (4.1, 301.4)=12.46, P<0.001). Mauchly's test indicated violation of the sphericity assumption

Table 5. Comparison of PCA pump usage parameters among groups within 48 hours after surgery

Parameters (48 hours)	PCA total required number of presses	Effective number of presses (times)	Actual administration frequency (times)	Single injection dose (mg/time)
Group C (n=50)	18.5±5.2	15.8±4.5	15.8±4.5	0.01 (Fentanyl)
Group O1 (n=50)	14.8±4.6	12.5±4.0	12.5±4.0	0.2
Group O2 (n=50)	9.6±3.8	8.2±3.1	8.2±3.1	0.35
P value (O2 vs. O1)	<0.001	<0.01	<0.01	-

Table 6. Comparison of Ramsay scores among groups at different time points

Group	Ramsay						
	T1	T2	T3	T4	T5	T6	T7
Group C (n=50)	2.36±0.53	2.28±0.55	2.10±0.60	2.03±0.57	1.90±0.55	1.83±0.60	1.74±0.65
Group O1 (n=50)	2.42±0.45	2.31±0.56	2.20±0.55	2.10±0.52	2.09±0.58	1.92±0.55	1.80±0.60
Group O2 (n=50)	2.58±0.40	2.43±0.45	2.30±0.50	2.20±0.59	2.13±0.55	2.03±0.55	1.92±0.63

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. Ramsay: Ramsay Sedation Scale. T1: 1 h postoperatively; T2: 2 h postoperatively; T3: 4 h postoperatively; T4: 8 h postoperatively; T5: 12 h postoperatively; T6: 24 h postoperatively; T7: 48 h postoperatively.

Table 7. Comparison of incidence of adverse reactions among groups

Group	Adverse event				
	Nausea	Vomiting	Dizziness	Respiratory depression	Hypoxemia
Group C (n=50)	4 (8.00)	3 (6.00)	3 (6.00)	1 (2.00)	2 (4.00)
Group O1 (n=50)	2 (4.00)	1 (2.00)	2 (4.00)	0 (0.00)	1 (2.00)
Group O2 (n=50)	3 (6.00)	2 (4.00)	4 (8.00)	0 (0.00)	1 (2.00)
P	0.718	0.647	0.718	1.000	1.000

Note: Using Fisher's exact test, Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group.

Table 8. Comparison of QoR-15 scores among groups at different time points among groups

Group	QoR-15		
	1 day before surgery	T6	T7
Group C (n=50)	117.36±9.57	88.20±12.18	98.46±11.39
Group O1 (n=50)	118.12±9.60	95.63±11.72	105.89±10.58
Group O2 (n=50)	117.58±9.43	101.97±10.85	111.24±9.86
F	0.033	19.324	23.768
P	0.968	<0.001	<0.001

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. QoR-15: Quality of Recovery-15.

(P<0.001), and the Greenhouse-Geisser correction was applied (ε=0.68). Post-hoc pairwise comparisons were performed using the Bonferroni method. It was found that the Ramsay sedation scores gradually declined from T1 to T7 in all three groups, indicating progressive recovery from sedation. Group O2 consistently showed higher Ramsay sedation scores throughout all evaluation periods compared with Groups C and O1, and the differences were statistically significant (*P*< 0.05).

Incidence of adverse events among the patient cohorts

The incidence of adverse events in the first 48 hours postoperatively is summarized in **Table 7**. In Group C, the incidences of nausea, vomiting, dizziness, respiratory depression, and hypoxemia were 8.0% (4/50), 6.0% (3/50), 6.0% (3/50), 2.0% (1/50), and 4.0% (2/50), respectively.

In Group O1, the incidence of nausea 4.0% (2/50), vomiting 2.0% (1/50), and dizziness 4.0% (2/50) were relatively lower than Group C, and no respiratory depression occurred. In Group O2, dizziness occurred in 8.0% (4/50), and the other adverse reactions were infrequent. Overall, the incidence of any adverse event showed no significant difference across the three groups (all *P*>0.05).

Table 9. Comparison of analgesic satisfaction among groups

Group	Satisfaction with pain relief				
	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied
Group C (n=50)	3 (6.00)	8 (16.00)	9 (18.00)	14 (28.00)	16 (32.00)
Group O1 (n=50)	2 (4.00)	4 (8.00)	7 (14.00)	18 (36.00)	19 (38.00)
Group O2 (n=50)	0 (0.00)	2 (4.00)	5 (10.00)	20 (40.00)	23 (46.00)
χ^2			18.746		
P			0.016		

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group.

Table 10. Comparison of serological indicators among groups at different time points among groups

Indicator	Group C (n=50)	Group O1 (n=50)	Group O2 (n=50)	*F*	*P*
IL-1β (pg/mL)					
1 day before surgery	3.26±1.14	3.15±1.05	3.25±1.08	0.112	0.894
T6	18.40±4.20	15.60±3.86	13.25±3.50	14.86	<0.001
T7	12.12±3.68	9.86±3.22	8.57±2.96	11.23	<0.001
IL-6 (pg/mL)					
1 day before surgery	4.50±1.27	4.45±1.15	4.55±1.18	0.067	0.935
T6	18.30±8.45	16.28±7.83	13.11±7.57	5.403	0.005
T7	11.10±8.92	8.60±7.36	6.32±6.82	4.78	0.01
TNF-α (pg/mL)					
1 day before surgery	12.80±0.94	12.75±0.85	12.85±0.92	0.132	0.877
T6	19.60±3.48	17.42±2.93	15.20±2.62	18.47	<0.001
T7	18.30±2.53	15.76±2.15	13.92±1.98	22.15	<0.001
MMP (ng/mL)					
1 day before surgery	125.05±25.03	124.54±24.87	126.06±25.24	0.038	0.962
T6	285.46±45.69	250.37±42.18	220.14±38.95	16.73	<0.001
T7	198.22±36.56	175.45±34.20	158.73±32.18	14.29	<0.001

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; MMP: Matrix Metalloproteinase.

QoR-15 scores in different groups at different time points

Table 8 presents QoR-15 scores of three groups at preoperative, postoperative day 1 and day 2. Preoperative QoR-15 scores were comparable across groups ($P>0.05$), indicating baseline equivalence. On postoperative day 1, Group C exhibited a markedly reduced QoR-15 score relative to both Group O1 and Group O2 ($P<0.001$). By postoperative day 2, QoR-15 scores in Group O2 showed greater recovery and were significantly higher than those in Group C and Group O1 ($P<0.001$), approaching preoperative baseline levels.

Analgesic satisfaction among groups

Table 9 shows patient-reported analgesic satisfaction across the three groups. A statistically significant difference was observed among the three groups ($P=0.001$). Patients in the Group O2 reported significantly higher satisfaction with postoperative analgesia compare with the other two groups.

Serological indicators in different groups at different time points

Changes in serum inflammatory factors and MMP levels among the three groups at one day before surgery, 24 hours postoperatively (T6), and 48 hours postoperatively (T7) are shown in **Table 10**.

Two-way repeated measures ANOVA was performed on these repeated measurement data. Taking IL-6 as an example, Mauchly's test of indicated a violation of the sphericity assumption ($P<0.001$), and the Greenhouse-Geisser

Table 11. Comparison of hemodynamic and respiratory parameters among groups at different time points

Indicator	Group C (n=50)	Group O1 (n=50)	Group O2 (n=50)	*F*	*P*
HR (Times/min)					
1 day before surgery	78.27±10.38	78.16±10.13	78.80±10.22	0.043	0.958
T6	85.42±12.16	82.36±11.52	80.17±10.82	4.52	0.013
T7	79.66±9.82	78.55±9.27	77.33±8.98	0.766	0.467
MAP (mmHg)					
1 day before surgery	92.43±10.55	92.67±10.20	92.14±10.37	0.029	0.971
T6	87.70±9.42	88.52±9.13	90.26±8.98	3.42	0.035
T7	91.27±9.66	91.88±9.37	92.52±9.12	0.681	0.508
RR (Times/min)					
1 day before surgery	18.50±2.38	18.32±2.18	18.47±2.26	0.084	0.92
T6	15.22±2.83	16.17±2.63	16.85±2.57	6.180	0.003
T7	17.38±2.47	17.51±2.36	18.50±2.20	3.400	0.036
SpO_2 (%)					
1 day before surgery	98.26±0.82	98.37±0.78	98.18±0.93	0.557	0.574
T6	97.45±1.28	97.08±1.16	98.06±1.08	8.46	<0.001
T7	97.69±1.02	97.92±0.95	98.22±0.89	3.62	0.029

Note: Group C: Fentanyl group; Group O1: Low-dose Oliceridine group; Group O2: High-dose Oliceridine group. HR: Heart rate; MAP: Mean arterial pressure; RR: Respiratory rate; SpO_2: Percutaneous oxygen saturation.

correction was applied (ε=0.71). The results showed a significant group × time interaction effect (F (2.8, 205.8)=18.77, *P*<0.001), as well as significant main effects of group (F (2, 147)=12.45, *P*<0.001) and time (F (1.4, 102.9)=45.32, *P*<0.001). Bonferroni post-hoc comparisons revealed significant differences in serum inflammatory factors and MMPs among the three groups across the observed time points. Preoperative levels of IL-1β, IL-6, TNF-α, and MMPs were comparable among the three groups (*P*>0.05), indicating baseline equivalence. At T6, serum levels of IL-1β, IL-6, TNF-α, and MMP were significantly elevated in Group C compared with the oliceridine groups. In contrast, Groups O1 and O2 showed attenuated postoperative inflammatory responses, with lower biomarker levels in Group O2 compared with Group O1 across all measured parameters. At T7, inflammatory markers remained elevated in Group C, whereas a further decline was observed in both Group O1 and O2.

Hemodynamic and respiratory parameters in different groups at different time points

Changes in hemodynamic and respiratory parameters among the three groups at one day before surgery, T6, and T7 are shown in **Table 11**. Repeated-measures ANOVA was performed separately for HR, MAP, RR, and SpO_2. Taking HR as an example, Mauchly's test indicated a violation of the sphericity assumption (*P*< 0.001), and the Greenhouse - Geisser correction was applied (ε=0.75). The results showed a significant group × time interaction effect (F (5.6, 411.6)=4.32, *P*=0.001), as well as significant main effects of group (F (2, 147)=4.32, *P*=0.015) and time (F (2.8, 205.8)=8.67, *P*< 0.001).

Bonferroni post-hoc comparisons revealed differences among the three groups at each time point. Preoperative hemodynamic and respiratory parameters, including HR, MAP, RR, and SpO_2, did not exhibit significant differences across the three groups (*P*>0.05). At T6, HR in Group C was significantly elevated compared with Groups O1 and O2 (*P*<0.05). In addition, RR and SpO_2 values in Group O2 were significantly improved compared with Group C (*P*< 0.05). At T7, Group O2 maintained relatively higher RR and SpO_2 values compared with Group C (*P*<0.05).

Usage of rescue analgesic medications

To further evaluate differences in postoperative analgesic requirements, the use of rescue analgesic drug (flurbiprofen axetil) within 24 hours postoperatively was analyzed.

Group O2 showed the lowest rate of rescue analgesic use, with an average number of rescue doses of 0.4±0.2, significantly lower than that in Group O1 (0.8±0.4) and Group C (1.2±0.6). Similarly, cumulative consumption of flurbiprofen axetil was significantly reduced in Group O2 compared with Group O1 and Group C (25.0±12.5 mg vs. 40.0±20.0 vs. 60.0±30.0 mg, $P<0.05$). These findings indicate that patients in the oliceridine high-dose group required fewer rescue analgesic interventions and lower cumulative NSAID consumption within the early postoperative period.

Discussion

Elderly patients with colorectal cancer are particularly susceptible to opioid-induced circulatory and respiratory depression due to decreased cardiopulmonary reserve and impaired drug metabolism [15]. Postoperative pain can activate the sympathetic nervous system, leading to increased heart rate and blood pressure fluctuations. Inadequate analgesia or excessive sedation may cause adverse outcomes such as arrhythmias, myocardial ischemia, or respiratory dysfunction [16]. Therefore, maintaining hemodynamic stability and adequate ventilation is essential for treatment safety [17]. In this context, effective analgesia in elderly patients may serve as a protective factor for respiratory and cardiovascular function. Huang et al. reported that PCIA with oliceridine was associated with a reduced incidence of opioid-related adverse drug events (ORADEs) compared with traditional opioids [18]. A study published in 2018 [19] further demonstrated that oliceridine reduced the incidence of postoperative nausea and vomiting. Although oliceridine may still cause nausea and vomiting, it is associated with an 18%-19% lower incidence of respiratory depression compared with morphine [20]. A prospective cohort study reported that the incidence of oliceridine-related respiratory events was approximately one-quarter of that observed with conventional opioids, with no reported fatal respiratory complications [21].

These findings are consistent with the pharmacological profile of oliceridine as a G-protein-biased μ-opioid receptor agonist, which provides effective analgesia while reducing β-arrestin-mediated adverse effects [22]. As a novel opioid receptor agonist, oliceridine has been reported to cause less respiratory depression and fewer gastrointestinal adverse reactions compared with traditional opioids [23]. Cao et al. showed that in postoperative pain management following laparoscopic cholecystectomy, the median effective dose (ED50) of oliceridine was 18.45 μg/kg, and the 95% effective dose (ED95) is 22.39 μg/kg, with analgesic efficacy improving in a dose-dependent manner without causing additional adverse reactions [24]. In addition, clinical studies on PCA have explored multiple demand doses of oliceridine (0.1 mg, 0.35 mg, and 0.5 mg), suggesting that dose adjustment is necessary to achieve effective postoperative analgesia [25].

This study systematically evaluated the perioperative outcomes of different dosages of oliceridine administered via PCIA compared to a traditional fentanyl-based PCIA regimen in elderly patients undergoing laparoscopic colorectal cancer resection. The results showed that the high-dose oliceridine group achieved significantly lower NRS-R and NRS-M scores, with a reduced incidence of moderate-to-severe pain. In addition, the high-dose regimen was associated with attenuation of postoperative inflammatory responses, improved hemodynamic and respiratory stability, earlier postoperative ambulation, and shorter hospital stays, without increasing the risk of severe adverse reactions.

A clear dose-dependent improvement in analgesic efficacy was observed with oliceridine. In Group O2, both NRS-R and NRS-M scores were significantly lower than those in Groups C and O1 across all time points, with the most obvious reduction observed during the 4-24 h postoperative window, corresponding to the peak pain period. Only 4% of the patients in Group O2 reported moderate-to-severe pain within 48 hours after surgery, significantly lower than that in Group C. In addition, this study suggests that oliceridine may modulate the postoperative inflammatory-stress responses in elderly patients with colorectal cancer. Serum levels of IL-6, TNF-α, and MMPs were significantly lower in Group O2 at 24 hours postoperatively compared with Group C, with a consistent dose-related reduction across groups.

Previous systematic reviews and meta-analyses have shown that oliceridol provides a rapid

onset analgesia in the postoperative pain setting that comparable to morphine [26]. Furthermore, in patients undergoing laparoscopic radical rectal cancer resection, oliceridine combined with sufentanil provided superior analgesia compared with sufentanil alone [27]. Mechanistically, oliceridine is a G protein-biased μ-opioid receptor agonist that preferentially activates G protein-dependent signaling pathways while reducing β-arrestin recruitment [28]. This biased signaling profile is considered to be the primary basis for its potent and sustained analgesic effects and its improved safety profile relative to conventional opioids [29]. Importantly, this study found that although the high-dose oliceridine group received a higher bolus concentration, total milligram consumption was lower compared with the low-dose group. This may be explained by improved analgesic efficiency at higher per-dose concentrations, facilitating reaching effective plasma levels more rapidly and maintaining more stable analgesia, thereby reducing the frequency of PCA demands and rescue dosing. Consequently, overall drug consumption decreased despite higher single-dose strength, suggesting that optimization of bolus dose rather than cumulative dose alone may improve analgesic efficiency and reduce unnecessary drug utilization.

Although the overall incidence of adverse events did not differ significantly among groups, dizziness was more frequently observed in Group O2 (8.0%) than in Group O1 (4.0%) or Group C (6.0%). While this difference was not statistically significant, likely due to limited sample size, it may still reflect a dose-related trend. Oliceridine, as a biased μ-opioid receptor agonist, is associated with reduced risk of respiratory depression; however, central nervous system-related adverse effects such as dizziness and nausea may still occur in a dose-dependent manner at higher exposure levels. The lack of statistical significance may be attributed to the relatively small sample size (n=50 per group), which limits the power to detect differences in low-frequency adverse events. Nevertheless, the numerically higher incidence of dizziness in Group O2 warrants clinical attention. These findings suggest that while high-dose oliceridine improves analgesia and reduces rescue analgesic requirements, it may increase the risk of mild central nervous system side effects. Therefore, individualized dose titration remains essential to balance analgesic efficacy and tolerability, rather than simply targeting the maximum tolerated dose.

Several limitations of this study should be acknowledged. First, even the sample size was pre-specified, this was a single-center study, which may limit the generalizability of this study. Therefore, future large-scale, multicenter randomized controlled trials are warranted to further validate the robustness of the results. Second, plasma drug concentration was not measured, precluding the establishment of a detailed pharmacokinetic-pharmacodynamic model. Third, the cost of oliceridine is higher than that of fentanyl, and a health economic evaluation was not performed. Furthermore, regarding opioid dose standardization, several methodological limitations should be noted. MME calculations have inherent limitations in equianalgesic conversion due to inter-individual variability in opioid responsiveness, differences in routes of administration and formulation. Moreover, as oliceridine is a novel G protein-biased μ-opioid receptor agonist approved in 2020, it has not yet been included in standard MME conversion tables issued by authoritative agencies such as the CDC. In the present study, an estimated MME conversion factor of approximately 13.3 for oliceridine was derived Based on preliminary experimental data and cross-validation using published data. Therefore, this MME values should be interpreted strictly as exploratory indicators of relative opioid exposure within this study cohort and should not be extrapolated as an absolute conversion standard. These MME values should be interpreted with caution and are not intended for cross-study comparisons. The primary conclusions regarding analgesic efficacy in this study were drawn from direct clinical endpoints (NRS scores, use of rescue analgesics, adverse reactions) rather than derived MME values.

Conclusion

High-dose oliceridine administered via patient-controlled intravenous analgesia provided clinical advantages in elderly patients undergoing laparoscopic colorectal cancer surgery. Compared with the low-dose oliceridine and fentanyl-based regimens, this high-dose strategy was associated with improved postoperative analgesia both at rest and during movement, as well as a lower incidence of moderate-to-severe pain.

In addition, high-dose oliceridine effectively suppressed the inflammatory response, improved hemodynamic and respiratory stability, earlier postoperative mobilization, and reduced length of hospital stay. It also contributed to improved quality of recovery and higher patient satisfaction, without increasing the risk of severe adverse reactions.

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Disclosure of conflict of interest

None.

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