

# Impact of Opioid-sparing Anesthesia on Postoperative Quality of Recovery in Patients undergoing Laparoscopic Colorectal Resection- A Randomized Controlled Trial

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## Article

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# Abstract

**Purpose:** Opioid analgesics may impair postoperative recovery and prolong hospital stay owing to common adverse effects, including opioid-induced hyperalgesia, postoperative nausea and vomiting, and shivering. This study aimed to evaluate the effects of a multimodal opioid-sparing anesthesia strategy on postoperative quality of recovery, perioperative hemodynamic profiles, and postoperative adverse events in patients undergoing laparoscopic colorectal resection, to further supplement clinical evidence for enhanced postoperative recovery management.

**Patients and methods:** 56 adult patients undergoing laparoscopic colorectal resection were randomly assigned to the multimodal opioid-sparing anesthesia group (Group OSA) or the conventional opioid-based anesthesia group (Group OA). The primary outcome was postoperative quality of recovery measured by the QoR-15 scale on postoperative day 2 (POD 2). Secondary outcomes included QoR-15 scores on postoperative day 7 (POD 7), visual analogue scale (VAS) pain scores recorded at 2, 4, 8, 24, and 48 hours postoperatively, 24-hour postoperative sufentanil consumption, intraoperative mean arterial pressure values, and the incidence of perioperative adverse reactions.

**Results:** Patients in Group OSA achieved significantly higher QoR-15 scores than Group OA at both POD 2 and POD 7: 110.0 (108.0, 111.0) vs. 89.0 (87.0, 91.0); 131.5 (130.0, 135.0) vs. 105.5 (105.0, 108.0),  $P < 0.001$ . VAS pain scores were significantly lower in Group OSA at 2, 4, 8 and 24 hours after surgery: 1 (1–2) vs 2 (2–3); 2 (1–2) vs 3 (2–3); 2 (2–3) vs 3 (2–3); 2 (1–2) vs 2 (2–3),  $P < 0.05$ . There was a significant difference in 24-hour postoperative sufentanil consumption and effective pressing times after surgery (77.5 (75.8, 80.0) vs. 65.0 (63.0, 66.0);  $2.8 \pm 0.5$  vs.  $2.5 \pm 0.5$ ,  $P = 0.05$ ) (Table 1). Mean arterial pressure (MAP) was significantly higher in Group OSA at pre-intubation (T1) and 1 min before skin incision (T3):  $84.3 \pm 3.1$  vs  $77.4 \pm 5.4$ ;  $83.0 \pm 2.5$  vs  $80.3 \pm 3.6$ ,  $P < 0.05$ . Patients in the OSA group also experienced a significantly lower incidence of nausea and vomiting compared to those in the OA group ( $P < 0.05$ ).

**Conclusion:** In conclusion, our findings suggest that multimodal opioid-sparing anesthesia may confer partial, time-limited benefits in early postoperative recovery quality for patients undergoing laparoscopic colorectal resection. Such benefits were largely driven by higher POD 2 global QoR-15 scores, whereas several secondary endpoints did not yield significant between-group differences. Additional investigations are needed to validate these results.

**Clinical Trial Registry:** ChiCTR2400081940 Date: March 15th, 2024

## 1. INTRODUCTION

Colorectal cancer (CRC) remains the third most commonly diagnosed cancer globally and accounts for approximately 10% of all tumor-related deaths<sup>1</sup>. Laparoscopic colorectal resection, while minimally invasive, still involves significant surgical trauma due to complex dissection within a well-innervated anatomical region<sup>2</sup>. This can lead to considerable physiological stress, delayed recovery, and increased

postoperative complications<sup>3</sup>. Enhancing recovery following such procedures remains a key clinical priority.

Opioid analgesics carry multiple undesirable perioperative side effects including hyperalgesia, postoperative nausea and vomiting, shivering and respiratory depression<sup>4</sup>. Although opioids are fundamental to general anesthesia for their potent analgesic and stress-reducing effects, their use is associated with well-documented adverse outcomes such as postoperative nausea and vomiting (PONV), respiratory depression, gastrointestinal dysfunction, and potential long-term use<sup>5</sup>. These complications may hinder the early postoperative recovery, which is crucial for the prognosis of patients and is not beneficial for patient recovery<sup>6-8</sup>.

Notably, evidence from randomized controlled trials supporting opioid-sparing anesthesia in laparoscopic colorectal surgery remains limited<sup>9-13</sup>. To address this gap, we designed a study comparing a structured low-opioid anesthesia protocol with conventional opioid-based anesthesia. We hypothesize that utilizing a low-opioid anesthesia technique – which combines multimodal agents (e.g., esketamine, dexmedetomidine, and regional techniques) to reduce opioid use – would result in improved postoperative recovery, superior analgesia, more stable hemodynamics, and fewer adverse effects compared to traditional opioid-based anesthesia in patients undergoing laparoscopic colorectal surgery.

## 2. METHODS

### 2.1. Patients and Study Design

This prospective, randomized, single-blinded clinical trial was conducted at the First People's Hospital of Lianyungang, China. Ethical approval was obtained from the Medical Ethics Committee of the First People's Hospital of Lianyungang (KY-20230920002-01) in September 2023, and the study was registered with the Chinese Clinical Trial Registry (ChiCTR) on March 15, 2024, registration number ChiCTR2400081940. Patient recruitment and data collection were performed from May 2024 to February 2025. All enrolled patients completed standardized perioperative observation and postoperative follow-up within 7 days after surgery. This study complied with the Declaration of Helsinki and was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

56 adult patients with ASA physical status I or II, aged 40–70 years, scheduled for laparoscopic colorectal resection were enrolled. Exclusion criteria were as follows: a. A history of allergy or contraindication to ropivacaine, esketamine) (e.g., significant risk of elevated blood pressure and intracranial pressure, poorly controlled or untreated hypertension, untreated or undertreated hyperthyroidism, gastrointestinal bleeding); b. Presence of mental illness and other chronic pain conditions or other conditions that may confound the analgesic response; c. Inability to read and write Chinese leading to communication barriers; d. Patients with severe cardiac and respiratory diseases; e. Patients with significant skin damage and infection in the ultrasound scan area; f. Reluctance to utilize intravenous pain relief pumps and refusal to participate.

## 2.2 Study Randomization

Patient allocation in this randomized controlled trial was determined by a computer-generated sequence with 1:1 allocation. To ensure concealment, the assignments were placed in sequentially numbered, opaque, sealed envelopes. These were opened by the anesthesiologist only after the patient entered the operating room, thereby disclosing the group assignment (OSA or OA). Group OSA received multimodal opioid-sparing anesthesia, defined as low-dose opioid general anesthesia combined with a transversus abdominis plane block, incision infiltration with local anesthetics, and postoperative analgesia via a patient-controlled analgesia (PCIA) pump. A research nurse, otherwise uninvolved in the study, was responsible for preparing all medications. Blinding was maintained for the patients, surgeons, nursing staff, postoperative outcome assessors, and the statistician. Due to the distinct drug administration regimens, the attending anesthesiologist was the only individual not blinded to the allocation.

## 2.3 Study Endpoints

The primary endpoint of this trial was defined as the quality of recovery on postoperative day 2, assessed using the 15-item Quality of Recovery (QoR-15) questionnaire. This comprehensive, patient-reported instrument evaluates five key recovery domains: physical comfort (5 items), emotional state (4 items), physical independence (2 items), psychological support (2 items), and pain (2 items). Each item is rated on a numerical scale from 0 to 10, with 0 representing a poor recovery and 10 representing an excellent recovery for that aspect. The cumulative scores from all items yield a total QoR-15 score, which ranges from 0 (poorest quality of recovery) to 150 (best quality of recovery).

The secondary outcomes included as follows: the pain visual analogue scores (VAS) were recorded at 2, 4, 8, 24, and 48 hours post-surgery. Additionally, The mean arterial pressure of the patients were recorded at baseline (T0), before intubation (T1), after intubation (T2), 1 min before skin incision (T3), 1 min after skin incision (T4), and at the end of the operation (T5). The incidence of perioperative adverse reactions including bradycardia, nausea and vomiting, dizziness, increased oral discharge, and respiratory depression was documented. It should be noted that nausea-and-vomiting-related information comes from two independent assessments. Item 3 of the QoR-15 scale reflects patients' subjective self-reported symptoms of nausea or vomiting at POD 2 and POD 7 as part of the recovery-quality questionnaire. By contrast, PONV listed among adverse events in Table 3 represents clinically defined postoperative nausea and vomiting episodes prospectively recorded by investigators within 48 hours after surgery. These two outcomes differ in evaluation window, evaluator and definition and are not duplicate analyses of identical data.

Furthermore, the utilization of sufentanil within the first 24 hours after surgery as well as the effective pressing times were assessed. Finally, variables such as length of hospital stay, time in PACU, first exhaust time were also recorded (Time in PACU: defined as the time from PACU admission until meeting discharge criteria -Aldrete score  $\geq 9$ ; First exhaust time: defined as the first passage of gas

postoperatively, reported by the patient or nursing records; Length of hospital stay: calculated from the day of surgery to the day of discharge.)

## 2.4 Anesthetic Management Protocol

All patients scheduled for elective laparoscopic colorectal resection were identified and visited according to standard protocols, based on predefined inclusion and exclusion criteria. Standard intraoperative monitoring was initiated upon arrival in the operating room, encompassing electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO<sub>2</sub>), and body temperature. In addition to these standard measures, the depth of anesthesia was monitored throughout the procedure using bispectral index (BIS) monitoring.

Pre-oxygenation was administered for 3 minutes before anesthesia induction. Group OSA received a pre-anesthesia dose of dexmedetomidine at a constant rate of 0.6 µg/kg, which was administered 10 minutes prior to induction. During the induction period, group OSA was given Remimazolam (0.2mg/kg), propofol (1-2mg/kg), atracurium cisenesulfonate (0.2mg/kg), sufentanil (0.2ug/kg), and esketamine (0.2mg/kg). Group OA was given Remimazolam (0.2mg/kg), propofol (1-2mg/kg), atracurium cisenesulfonate (0.2mg/kg) and sufentanil(0.4ug/kg). Anesthetic maintenance period: Group OSA received propofol at a dosage of 4-6mg/kg/h, dexmedetomidine at a dosage of 0.1-0.2ug/kg/h, and esketamine at a dosage of 0.2-0.3mg/kg/h. Group OA received propofol at a dosage of 4-6mg/kg/h and remifentanyl at a dosage of 0.1-0.3ug/kg/min. Both groups were administered sevoflurane inhalation anesthesia with concentrations ranging from 1% to 3%.

In adult patients undergoing general anesthesia with endotracheal intubation, implement intraoperative mechanical ventilation using Pressure Control Volume Guaranteed (PCV-VG) mode. Set initial tidal volume to 6–8 mL/kg predicted body weight and respiratory rate to 12–20 breaths/min. Adjust sevoflurane concentration in an oxygen/air mixture (FiO<sub>2</sub> 0.6, total gas flow 2 L/min) to maintain BIS values between 40 and 60, targeting a MAC range of 0.8–1.4. Continuously monitor PetCO<sub>2</sub> and maintain it within 35–40 mmHg, while ensuring peak airway pressure remains below 30 cm H<sub>2</sub>O. Regularly assess ventilatory and hemodynamic parameters every 5 minutes and adjust settings accordingly to ensure physiological stability throughout surgery.

After surgery, the surgeon used 0.375% ropivacaine for local infiltration anesthesia in each endoscopic incision. In the two group, participants received transversus abdominis plane (TAP) block (20 ml 0.375% ropivacaine for each side). In addition, both groups of patients received patient-controlled intravenous analgesia (PCIA). In group OSA, the analgesic pump formula consisted of sufentanil 1ug/kg + esketamine 1.0mg/kg + Tropisetron 10mg (diluted with normal saline to a total volume of 100ml). The background infusion rate was set at 2ml/h, each compression delivered 2ml, and there was a locking time of 10 minutes. In group OA, the analgesic pump formula included Sufentanil 2ug/kg + Tropisetron 10mg (diluted with normal saline to a total volume of 100ml). The background infusion rate was also set at 2ml/h, each compression delivered 2ml, and there was a locking time of 10 minutes. Following

surgery, suspend PCIA infusion if the patient's VAS score  $\geq 1$  and exhibits respiratory depression, confusion, blood pressure instability, or other conditions that hinder continued use of the analgesic pump. All patients received patient-controlled intravenous analgesia (PCIA) for 48 hours after surgery. The PCIA pump was continuously maintained throughout postoperative 48 h .

Hypotension, defined as a systolic blood pressure reduction of more than 20% from the preoperative baseline or a systolic blood pressure below 90 mmHg, was managed with intravenous norepinephrine at a dose of 4–8  $\mu$ g during the period from anesthesia induction to discharge from the post-anesthesia care unit (PACU). Bradycardia, defined as a heart rate reduction exceeding 20% from the preoperative baseline or a heart rate below 50 beats per minute (bpm), was treated with 0.5 mg of intravenous atropine.

## 2.5 Data Analysis

QoR-15 was chosen as the primary outcome on POD 2 after surgery. Previous literature reports <sup>30</sup> indicate that the QoR-15 score of  $70.6 \pm 13.7$  is typical for patients undergoing colorectal surgery on the second day post-operation, and an average difference of at least 12 points is considered clinically significant. The bilateral significance and efficacy were set at 0.05 and 80%, respectively, and G-power software was utilized to calculate a required sample size of 22 patients per group. Accounting for an estimated dropout rate of approximately 15%, we plan to enroll a total of 56 patients. Dataset analysis was conducted using SPSS Statistics (Version 25.0). The distribution of continuous and ordinal variables was studied using the Shapiro–Wilk test. Continuous variables with a normal distribution are presented as mean  $\pm$  SD and analyzed with the independent samples t-test, while skewed data are presented as median (IQR) and analyzed with the Mann-Whitney U test. Categorical variables are presented as n (%) and analyzed with Pearson's chi-square test. A two-tailed p-value  $< 0.05$  was deemed statistically significant.

## 3. RESULTS

### 3.1. Recruitment Process

The details of the study cohort conduction are shown in Figure 1. 56 adult patients underwent laparoscopic colorectal resection at our hospital. Of these, 4 patients were excluded; 3 because of not meeting inclusion criteria, 1 because of declining to participate. Among 52 patients included in this analysis, 26 received intraoperative OA anesthesia method and 26 received intraoperative OSA anesthesia method (Figure 1).

Figure 1. Flow diagram of the study patients.

### 3.2. Demographic and Clinical Characteristics

No difference in age, gender, BMI, American Society of Anesthesiologists (ASA), anesthesia duration and operation duration, time in PACU, length of stay, the first exhaust time and effective pressing times were identified between the two groups. There were significant difference in 24-hour postoperative sufentanil consumption and effective pressing times after surgery (77.5(75.8, 80.0) vs. 65.0(63.0, 66.0) ; (2.8±0.5 vs. 2.5±0.5  $P=0.05$ ) (Table 1).

**Table 1** Patient characteristics and perioperative data.

| Characteristic                                | Group OA(n=26)   | Group OSA(n=26)  | P value |
|-----------------------------------------------|------------------|------------------|---------|
| Demographic Features                          |                  |                  |         |
| Age (yr)                                      | 61.5±6.3         | 60.5±7.2         | 0.259   |
| Gender, n (%)                                 |                  |                  |         |
| Male                                          | 12(46.2)         | 14(53.8)         | 0.579   |
| Female                                        | 14(53.8)         | 12(46.2)         |         |
| BMI ( kg/m <sup>2</sup> )                     | 21.5±1.1         | 21.8±1.0         | 0.332   |
| ASA physical status, n (%)                    |                  |                  |         |
| I                                             | 15(57.7)         | 16(61.5)         | 0.777   |
| II                                            | 11(42.3)         | 10(38.5)         |         |
| Perioperative data                            |                  |                  |         |
| Anesthesia duration (min)                     | 126.0±3.9        | 124.8±3.2        | 0.363   |
| Operation duration (min)                      | 99.7±4.9         | 98.0±5.6         | 0.774   |
| Time in PACU (min)                            | 35.1±1.3         | 34.3±1.9         | 0.087   |
| length of hospital stay (d)                   | 6.5±0.9          | 6.0±0.7          | 0.108   |
| Use of sufentanil 24 hours after surgery (ug) | 77.5(75.8, 80.0) | 65.0(63.0, 66.0) | 0.001*  |
| Effective pressing times                      | 2.8±0.5          | 2.5±0.5          | 0.008 * |
| First exhaust time(days)                      | 3.0±0.5          | 2.7±0.5          | 0.081   |

**Notes:** \* $p<0.05$ . Data are expressed as mean±SD, median (interquartile range) or number (percentage).

**Abbreviations:** OSA: Opioid-sparing anesthesia; OA:Opioid anesthesia; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; PACU: Post-anesthesia care unit. Effective pressing time: the total number of valid PCIA button presses triggered by patients within 24 hours after surgery. Each valid press means the patient received a standard rescue sufentanil dose from the PCIA pump.

3.3 Visual Analogue Scale (VAS) Assessment

Postoperative pain intensity, as assessed by the Visual Analogue Scale (VAS), was significantly lower in the OSA group than in the OA group at 2, 4, 8, and 24 hours after surgery (all  $P < 0.05$ )(Table 2).

Table 2 VAS scores.

| VAS | Group OSA(n=26) | Group OA(n=26) | P value |
|-----|-----------------|----------------|---------|
| 2h  | 1(1-2)          | 2(2-3)         | <0.001* |
| 4h  | 2(1-2)          | 3(2-3)         | <0.001* |
| 8h  | 2(2-3)          | 3(2-3)         | 0.019*  |
| 24h | 2(1-2)          | 2(2-3)         | <0.001* |
| 48h | 1(1-1)          | 1(1-2)         | 0.081   |

**Notes:** \* $p \leq 0.05$ . Data are expressed as median (interquartile range).

**Abbreviations:** OSA: Opioid-sparing anesthesia; OA:Opioid anesthesia; VAS: Visual Analogue Scores.

3.4 Perioperative Adverse Reactions

Patients in the OSA group also experienced a significantly lower incidence of nausea and vomiting compared to those in the OA group (all  $P < 0.05$ ). In contrast, no statistically significant differences were observed between the two groups in terms of lightheadedness, increased oral secretion and respiratory depression(Table 3).

Table 3 Perioperative adverse reactions.

| Perioperative adverse reactions<br>n (%) | Group OA(n=26) | Group OSA(n=26) | P value |
|------------------------------------------|----------------|-----------------|---------|
| Nausea                                   | 8(30.8)        | 2(7.7)          | 0.035*  |
| Vomiting                                 | 6(23.1)        | 1(3.8)          | 0.042*  |
| Feeling lightheaded or dizzy             | 4(15.4)        | 1(3.8)          | 0.158   |
| Increased oral discharge                 | 1(3.8)         | 5(20.0)         | 0.073   |
| Respiratory depression                   | 4(15.4%)       | 2(7.7%)         | 0.667   |

**Notes:** \* $p \leq 0.05$ . Data are expressed as number (percentage).

**Abbreviations:** OSA: Opioid-sparing anesthesia; OA: Opioid anesthesia; All adverse reactions were recorded within 24 hours postoperatively. Respiratory depression was defined peripheral oxygen saturation less than 95% and/or respiratory frequency less than 12 breaths per minute, excluding patients with chronic underlying respiratory disorders.

### 3.5 The QoR-15 Score

The QoR-15 score was markedly better in the OSA group than in the OA group on POD2 and POD7 (110.0(108.0,111.0) vs. (89.0(87.0,91.0); 131.5(130.0,135.0) vs. 105.5(105.0,108.0),  $P < 0.001$ ).

These differences of 21 and 26 points are clinically meaningful, as they greatly surpass the MCID of 8.0 for the QoR-15 scale. Group OA demonstrated notably lower scores on POD2 and POD7 for postoperative pain, physical comfort, physical independence, psychological support and emotional state dimensions compared to group OSA (13.0(12.0,14.0) vs. 16.0(15.0,16.0), 16.0(15.0,16.0) vs. 18.0(18.0,18.3), and  $P < 0.001$ ; 21.0(20.0,22.0) vs. 28.5(28.0,30.0), 25.5(25.0,27.0) vs. 38.0(38.0,40.0) and  $P < 0.001$ ; 13.0(13.0,14.0) vs. 15.0(14.0,15.0), 17.0(17.0,18.0) vs. 20.0(19.0,20.0) and  $P \leq 0.001$ ; 15.0(15.0,16.0) vs. 18.0(17.0,18.0), 17.0(16.0,17.0) vs. 19.0(18.0,20.0) and  $P \leq 0.001$ ; 26.0(26.0,27.00) vs. 32.0(31.0,33.0), 30.0(30.0,33.0) vs. 37.0(36.0,38.0) and  $P \leq 0.001$ ) (Figure 2).

Figure 2. There was a significant change in the global scores, physical comfort, physical independence, psychological support, pain, and emotional state on POD2 and POD7 ( $P < 0.05$ ). Non normal distribution measurements were expressed as medians and interquartile ranges.  $P < 0.05$  was considered to be statistically significant.

### 3.6 Mean Arterial Pressure (MAP)

The mean arterial pressure (MAP) in group OSA was higher than that in group OA at the time of before intubation (T1) and 1 min before skin incision (T3) ( $84.3 \pm 3.1$  vs.  $77.4 \pm 5.4$ ;  $83.0 \pm 2.5$  vs.  $80.3 \pm 3.6$ ,  $P < 0.05$ ). (Figure 3).

Figure 3. Perioperative mean arterial pressure (MAP) at baseline (T0), before intubation (T1), after intubation (T2), 1 min before skin incision (T3), 1 min after skin incision (T4), and at the end of the operation (T5); \*P<0.05.

## 4. DISCUSSION

In this single-center randomized controlled trial involving patients undergoing laparoscopic colorectal resection, we found that multimodal opioid-sparing anesthesia (OSA) was associated with improved early postoperative recovery quality.

Our results demonstrated that the multimodal OSA regimen yielded a more favorable early recovery profile compared with conventional opioid-based anesthesia (OA). Specifically, patients in the OSA group achieved significantly higher global QoR-15 scores on postoperative day 2, and the intergroup difference exceeded the established minimal clinically important difference (MCID) of 8.0 for this scale<sup>14–15</sup>. These beneficial early recovery outcomes may be attributable to the multimodal pharmacological characteristics of the OSA strategy. Dexmedetomidine exerts natural sleep-like sedation via  $\alpha_2$ -adrenergic agonism, which may attenuate postoperative stress responses<sup>16</sup>. Additionally, esketamine may contribute to improved postoperative psychological recovery, given its documented rapid antidepressant effects in clinical settings, which may partially explain the superior emotional recovery metrics observed in the OSA group. Collectively, these findings suggest that multimodal opioid-sparing anesthesia may provide perioperative benefits beyond pain control and may favorably influence early postoperative neuropsychological recovery. Nevertheless, these observations require further verification in larger, multicenter trials to confirm long-term clinical implications<sup>17–18</sup>. Our results are partially consistent with previous findings reported by Bekker et al., who demonstrated improved postoperative recovery quality, emotional status, and psychological support in patients receiving optimized anesthesia for spinal surgery<sup>19</sup>.

In terms of pain recovery, the OSA group exhibited superior QoR-15 pain dimension scores and significantly lower peak VAS pain scores within 2h, 4h, 8h and 24 h after surgery, alongside reduced 24-hour sufentanil consumption. These findings are consistent with previous evidence showing that esketamine alleviates moderate-to-severe postoperative pain and improves patient-reported pain outcomes<sup>20</sup>. The pain-sparing effects observed in the OSA group may counteract remifentanyl-induced hyperalgesia commonly encountered in opioid-based anesthesia. Opioid-induced hyperalgesia is thought to involve central NMDA receptor-mediated neuronal sensitization, which can be ameliorated by NMDA antagonists such as esketamine<sup>21</sup>. Furthermore, dexmedetomidine suppresses neuronal excitation and inhibits the release of pronociceptive neurotransmitters via  $\alpha_2$ -adrenergic activation, thereby facilitating analgesia and stabilizing perioperative pain transmission<sup>22</sup>.

Consistent with the reduced opioid consumption in the OSA group, we observed a numerically lower incidence of PONV in OSA patients, although no significant difference in respiratory depression was detected between groups in our cohort. Previous studies have reported that esketamine may reduce

hypoxemia and intraoperative carbon dioxide accumulation without inducing respiratory depression<sup>23–24</sup>. Multiple clinical trials have demonstrated reduced PONV rates with esketamine-dexmedetomidine-based opioid-sparing regimens in abdominal and thoracic surgery patients<sup>25</sup>. Furthermore, opioid-sparing anesthesia protocols have been shown to facilitate early oral intake and enhance ERAS-compliant postoperative recovery<sup>26</sup>. However, our negative findings regarding respiratory depression indicate that the respiratory protective advantages of OSA observed in previous studies were not replicated in our laparoscopic colorectal surgical population.

Anesthesia-induced hypotension, commonly observed during the induction of opioid-based anesthesia, may increase the risk of myocardial injury by decreasing myocardial perfusion and oxygen delivery<sup>27</sup>. In our study, MAP values were significantly lower in the OA group relative to the OSA group at T1 and T3, whereas no statistically-significant intergroup differences in MAP were detected at other measured time points. These between-group discrepancies limited to T1 and T3 may be partially attributed to the pharmacological features of the study regimens. Dexmedetomidine suppresses neuronal firing and exerts sedative, analgesic, and anti-sympathetic effects, which may help mitigate blood-pressure decline during specific induction-related phases<sup>28</sup>. A second plausible factor is the mild sympathomimetic effect of esketamine. Together with its analgesic and sedative actions, esketamine may lower the requirement for other anesthetic agents, which could partly account for the intergroup MAP difference observed at T1 and T3<sup>29</sup>.

This study has several limitations. First, the single-center design may introduce selection bias and limit the generalizability of the findings. Second, postoperative recovery quality was only evaluated on POD 2 and POD 7, and longer-term recovery trajectories remain unexplored. Third, this study adopted a fixed-dose combination of esketamine and dexmedetomidine, prohibiting dose-response and subgroup analyses. Fourth, multiple non-opioid adjuvants were applied simultaneously in the OSA group with reduced sufentanil dosage; therefore, the independent effect of opioid reduction cannot be isolated, and all observed differences should be interpreted as the comprehensive effects of multimodal anesthesia. Fifth, multiple secondary outcomes were analyzed without correction for multiple comparisons, which may increase the risk of type I error. Sixth, blinding of anesthesiologists was not feasible due to distinct pharmacological profiles of the study regimens, potentially leading to performance bias. In addition, several patient-reported and safety outcomes, including postoperative dizziness, increased oral discharge, 48-hour peak VAS pain scores, and respiratory depression, showed no significant differences between groups, further indicating that the benefits of the OSA regimen were partial and time-specific rather than universal.

## 5. CONCLUSIONS

In conclusion, our findings suggest that multimodal opioid-sparing anesthesia may confer partial, time-limited benefits in early postoperative recovery quality for patients undergoing laparoscopic colorectal resection. Such benefits were largely driven by higher POD 2 global QoR-15 scores, whereas

several secondary endpoints did not yield significant between-group differences. Additional investigations are needed to validate these results.

## **Declarations**

### **Authors' contributions**

Hengfei Luan has made substantial contributions to the conception or the design of the manuscript, Jiying Feng, Pin Zhu and Yong Wu to patient recruitment, Conghui Hao and Xiaobao Zhang to manuscript writing, Yunyan Wang to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, Hengfei Luan revised it critically. All authors read and approved the final version of the manuscript.

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### **Availability of data and materials**

The datasets generated and analysed during this randomised controlled trial are not publicly available due to patient-privacy restrictions and ethical-approval constraints. De-identified minimal study data underlying the reported findings (including the QoR-15 dataset) are available from the corresponding author upon reasonable written request and subject to a formal data-sharing agreement.

### **Ethics approval and consent to participate**

Ethical approval for this study was provided by the Medical Ethics Committee of the First People's Hospital of Lianyungang on November 16, 2023. Written informed consent was obtained from all study participants. All procedures performed in this study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments .

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare no competing interests.

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## Figures

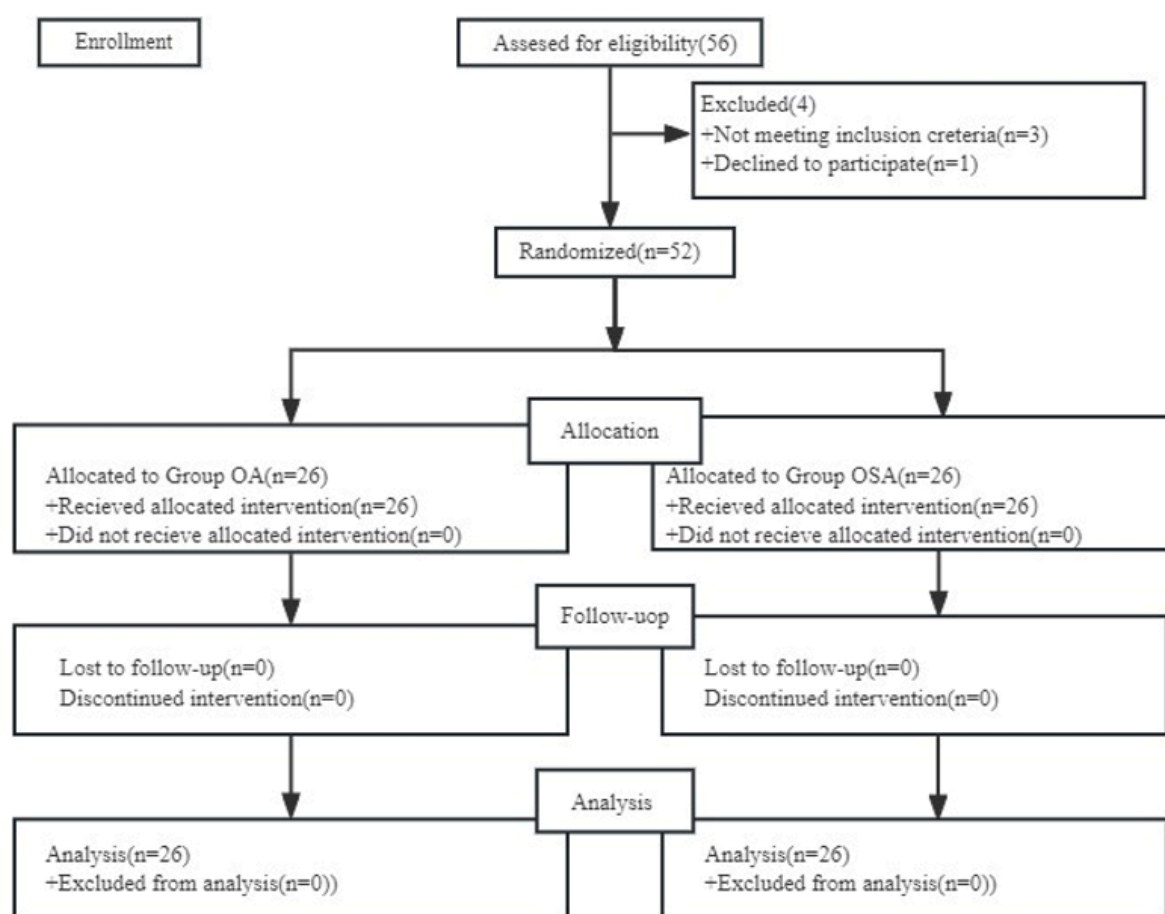


**Figure 1**

Flow diagram of the study patients.

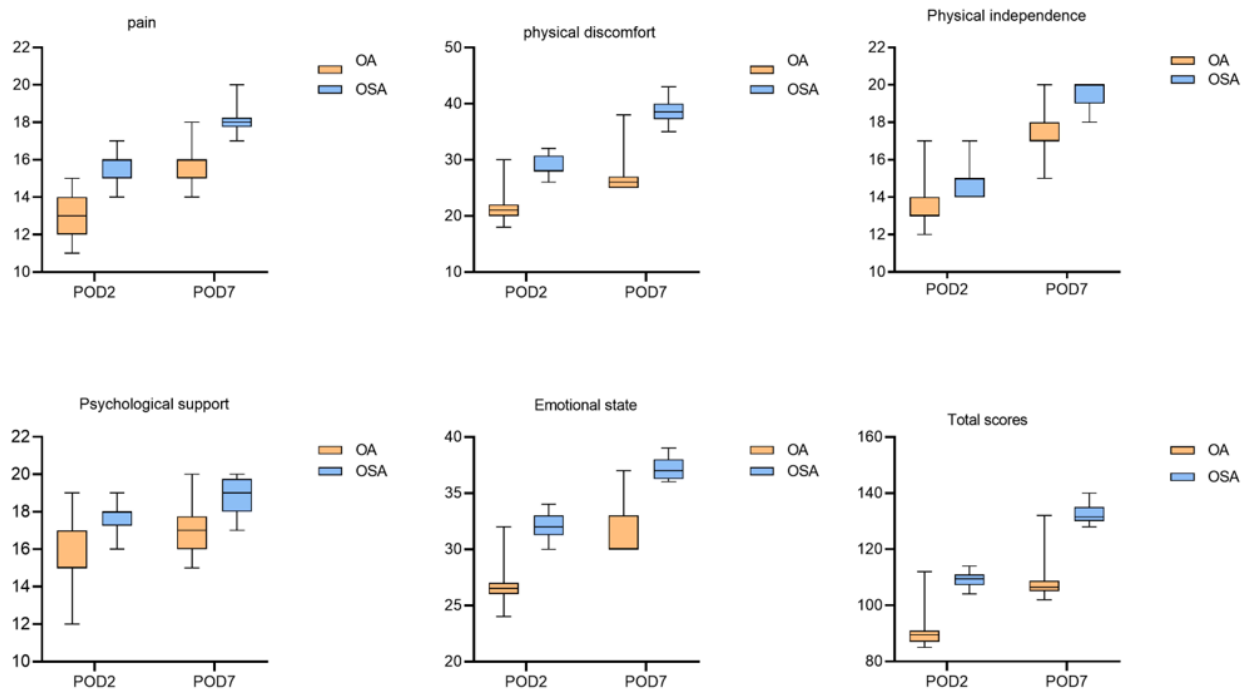


**Figure 2**

There was a significant change in the global scores, physical comfort, physical independence, psychological support, pain, and emotional state on POD2 and POD7 ( $P < 0.05$ ). Non normal distribution measurements were expressed as medians and interquartile ranges.  $P < 0.05$  was considered to be statistically significant.

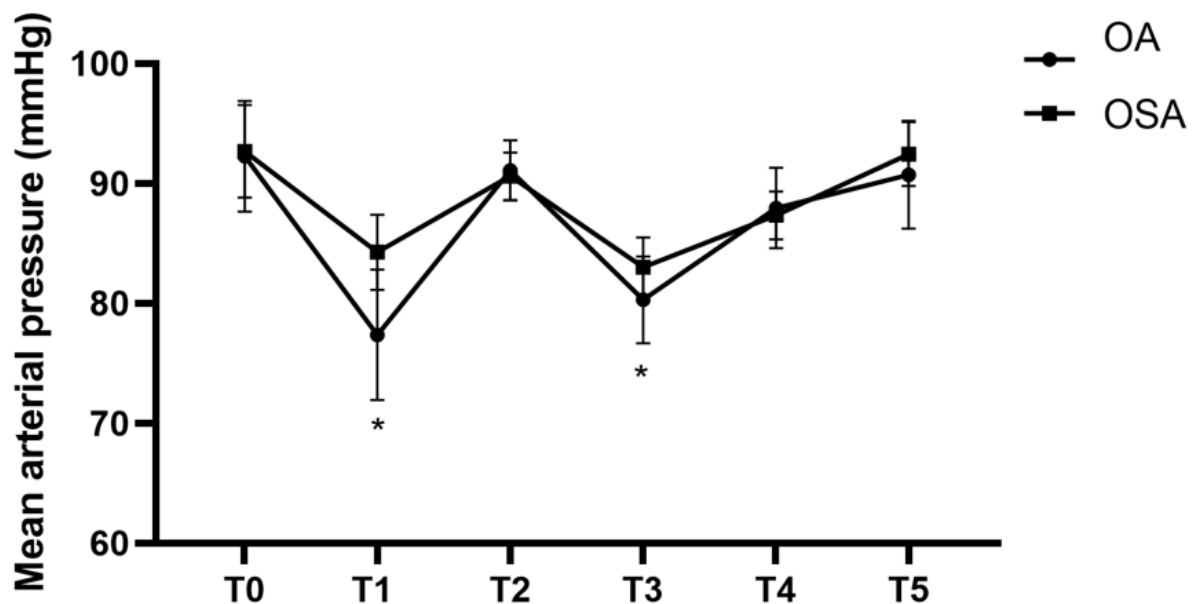


**Figure 3**

Perioperative mean arterial pressure (MAP) at baseline (T0), before intubation (T1), after intubation (T2), 1 min before skin incision (T3), 1 min after skin incision (T4), and at the end of the operation (T5); \*P<0.05.

## Supplementary Files

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- [CONSORTchecklist.docx](#)