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CLINICAL TRIAL REPORT

The Opioid-Sparing Effects of Intraoperative Esketamine Combined with Dexmedetomidine During Laparoscopic Major Abdominal Surgery: A Randomized Controlled Double-Blind Trial

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Background: Recently, opioid-sparing (OS) interventions have been proposed to facilitate rapid postoperative recovery for patients. However, the advantages of OS anesthesia strategy in laparoscopic abdominal major surgery are still unknown.

Methods: 157 patients undergoing laparoscopic major abdominal surgery were randomly assigned to two groups: Remi (77, remifentanil) and OS (80, esketamine combined with dexmedetomidine), the drugs were administered at 0.2-0.5 mg/kg/h (remifentanil or esketamine) and 0.2-0.7μg/kg/h (remifentanil or dexmedetomidine) in two syringes, respectively The primary outcome was the numeric rating scale (NRS) pain score on postoperative day (POD)1. The proportion of rescue analgesia within 48 h, extubation time, postoperative quality recover scale (PQRS), Pittsburgh Sleep Quality Index (PSQI) on POD30 were also recorded.

Results: In the postanaesthesia care unit (PACU), the NRS pain score and the proportion of rescue analgesia in Remi group was significantly higher than that in OS group (3 [1 to 3] vs 1 [1 to 3], $P = 0.001$; 15.6% vs 5.0%, $P = 0.028$, respectively), although there were no statistical differences in NRS pain score on POD1, POD7 and POD30 between groups (3 [2 to 3] vs 3 [2 to 3], $P = 0.648$; 2 [1 to 2] vs 2 [1 to 2], $P = 0.418$; 0 [1 to 1] vs 0 [1 to 1], $P = 0.656$, respectively). The extubation time in the OS group was longer and the proportion of dreaminess was also higher than that in the Remi group (20 [11 to 34] vs 31 [21 to 40], $P < 0.01$; 15.6% vs 42.5%, $P < 0.01$), However, the PSQI on POD30 were similar between groups (8.27±3.94 vs 8.37±3.89, $P = 0.870$).

Conclusion: In this study, OS anesthesia strategy during laparoscopic major abdominal surgery decreases the NRS pain scores in PACU and reduces the use of rescue analgesia, though it may prolong the extubation time and increase the proportion of dreaminess during hospitalization.

Trial Registration Number: ChiCTR2200060130.

Keywords: opioid-sparing anesthesia, esketamine, dexmedetomidine, laparoscopic major abdominal surgery

Introduction

Opioids and their derivatives constitute the gold standard for the treatment of moderate to severe pain and are employed for pain management during the perioperative period.[1] However, perioperative utilization of opioids has also lead to many adverse reactions, including nausea and vomiting, gastrointestinal paralysis, delirium, respiratory depression, and even promotes the proliferation and metastasis of cancer cells.[1,2] Adequate pain management can be achieved not only with opioids, but also with non-opioid analgesics and local anesthesia. Therefore, the concept of opioid-sparing (OS)

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anesthesia has been proposed, which refers to the composite anesthesia mode formed by the combination of a variety of non-opioid analgesics and regional block anesthesia techniques.[3] The combinations of intravenous lidocaine,[4] ketamine, dexmedetomidine and magnesium sulfate[5] were the most commonly utilized in the last 30 years. More and more studies have shown that an OS anesthesia approach reduces the consumption of opioids perioperatively, thus improving the quality of postoperative recovery.[6–8]

Esketamine is an s-enantioisomer of ketamine, with a greater affinity to the N-methyl-D-aspartate receptors (NMDARs), whose analgesic efficacy is approximately 1.5 to 2 times that of ketamine with fewer side effects. Due to the unique pharmacological advantages, esketamine has become the most appealing adjuvant anesthetic.[9,10] Dexmedetomidine is a novel alpha-2 adrenergic activating sedative with analgesic and antiemetic effects, and has been widely used perioperatively. Several studies have shown that even low doses of dexmedetomidine during the operation significantly reduce the consumption of opioids and have little effect on respiration.[11–13]

The postoperative quality recover scale (PQRS) is a brief tool that enables the assessment of recovery in multiple domains and over multiple time periods, including the scores of physiological, emotional, activities of daily living, cognitive and overall patient perspective.[14,15]

Our hypothesis is that esketamine combined with dexmedetomidine is a safe and effective opioid-sparing anesthesia strategy in laparoscopic major abdominal surgery and it may improve the quality of postoperative recovery. The main objective of the present randomized double-blind trial was to evaluate the feasibility and the OS effects of the combination of esketamine and dexmedetomidine in patients undergoing laparoscopic major abdominal surgery, so as to provide clinical reference for the optimal anesthetic strategy.

Methods

Study Participants

This trial is compliant with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[16] The study was carried out in accordance with the Declaration of Helsinki and registered at the Chinese Clinical Trial Registry and implemented from 6 May 2022 to 23 August 2023. Informed consent was obtained from each patient who agreed to participate in the study one day before surgery.

The inclusion criteria included patients undergoing laparoscopic major abdominal surgery (operations requiring a gastrointestinal anastomosis or involving bowel resection or parenchymal resection of the liver or pancreas; surgery time >2 h),[17,18] aged 18–65 years, BMI 18.5–28 kg/m^2 and American Society of Anesthesiologists (ASA) classification: Grade I–III. The exclusion criteria were as follows: severe neurological, hepatic, renal or autoimmune diseases; malignant tumors in multiple organs or distant metastases; preoperative radiotherapy, chemotherapy or immunotherapy; glucocorticoid or immunosuppressive therapy within 1 year; history of major surgery within 1 year; SBP/DBP >180/110 mmHg; HR <50 bpm or >100 bpm; patients with hyperthyroidism or hypothyroidism. All patients did not take analgesics preoperatively.

Randomisation and Blinding

Participants were randomly divided into the remifentanil group (Remi group) and opioid-sparing group (OS group, esketamine combined with dexmedetomidine) by using a computer-generated list of random numbers (1:1 ratio). The random numbers were sealed with opaque envelopes to conceal arm allocation. The envelopes were opened in sequence by an unsuspecting assistant, who extracted the drugs and handed them to the researchers. Patients, anesthesia providers, surgeons, operating room nurses, and outcome assessors were all blinded to the group allocation.

Anesthesia Protocol

No patient has preoperative medication. Each participant entered the operating room, and routine monitoring including blood pressure (BP), peripheral oxygen saturation (S_PO_2), heart rate (HR) and Narcotrend index (NI) monitoring were established. Ultrasound-guided puncture catheter was inserted into the right internal jugular vein and radial artery, then stroke volume variation (SVV), stroke volume (SV), cardiac output (CO), cardiac index (CI) and systemic vascular

resistance index (SVRI) was monitored by Most-care or Vigileo. The baseline values were recorded routinely. All participants received preoxygenation with 100% oxygen for 3–5 minutes using a face mask. Sufentanil 0.3 μg/kg, propofol (TCI 3 ug/mL) and cis-atracurium 0.2 mg/kg were intravenously injected for induction of anesthesia. Tracheal intubation was performed when the patient lost consciousness and the jaw was relaxed. After endotracheal intubation, an anesthesia machine was connected for mechanical ventilation. The end-tidal CO_2 pressure ($P_{ET}CO_2$) was maintained between 35 and 45 mmHg by adjusting tidal volume (6–8 mL/kg) and respiratory rate (12–16 beat/min). The fraction of inspired oxygen was set at 60%. Propofol of TCI 2–5 μg/mL and cis-atracurium 1.5 μg/kg/min were infused and 1–2% sevoflurane was inhaled to maintain anesthesia intraoperatively. Hemodynamic variables were maintained within 20% of the baseline measurements. Each group was continuously infused with drug X [remifentanil (20 ug/mL) or esketamine (1 mg/mL)] with 0.2–0.5 mg/kg/h and drug Y [remifentanil (20 ug/mL) or dexmedetomidine (4 μg/mL)] with 0.2–0.7 ug/kg/h after anesthesia induction until 10 min before completion of the operation. The anesthesiologist tailored the rate of drug administration based on the patient's vital signs. Propofol and sevoflurane were discontinued at the end of skin suture. Ondansetron 4 mg was administered intravenously to prevent postoperative nausea and vomiting. After the operation, patients were transferred to the postanesthesia care unit (PACU) and continuously observed until they left the PACU.

Primary and Secondary Outcomes

Pain score was evaluated by the numeric rating scale (NRS) postoperatively (PACU, postoperative day (POD)1, POD7 and POD30, respectively. With 0, painless; 10, worst imaginable pain). The primary outcome was an NRS pain score on POD1. Patients were administered nonsteroidal analgesics, tramadol or opioids when the NRS pain scores were ≥4.

Secondary outcomes were the proportion of PACU rescue analgesia and the proportion of ward rescue analgesia within 48 h. Extubation time, postoperative quality recover scale (physiology, nociceptive, emotional, activities of daily living, cognitive and overall patient perspective; PQRS),[14] Pittsburgh Sleep Quality Index (PSQI) at POD30 and other outcomes (consumption of anesthetics, proportion of vasoconstrictor, proportion of atropine and intraoperative vital signs, postoperative hospitalization days, postoperative complications within 30 days) were also recorded.

Sample Size Calculation

According to previous studies,[19] assuming that the proportion of rescue analgesia (NRS pain score >4) was 85% in the conventional opioid group, and 65% in the OS group (the postoperative NRS score of the OS group decreased by 50%).[7] Using a two-sided alpha risk of 5% with a statistical power of 80%, and the loss of follow-up rate is expected to be 10%. The required sample size for each group is 76 patients.

Statistical Analysis

SPSS, version 19.0 statistical software was used for statistical analysis. The Shapiro–Wilk test was used to assess data distribution. Results for normally distributed data for quantitative variables were expressed as mean ± standard deviation (SD), non-normal distributed data were expressed as median [interquartile range (IQR)] and for qualitative variables as a percentage. Student's *t* test was used for normally distributed data, and the Mann–Whitney *U*-test was used for nonparametric data. Pearson's chi-squared test or Fisher's exact test was used for qualitative variables. The generalized estimation equation (GEE) was allowed for analysis of repeated measurements. Repeated measure variables were expressed as estimated marginal mean (EMM) [95% confidence interval (95% CI)] and the working correlation matrix structure was independent structure and the regression model was the linear regression model. Type I errors were controlled using the Bonferroni method, which adjusted the *P*-value by multiplying the nominal *P*-value by the number of tests. All statistical tests were conducted by bilateral tests, and a *P*-value less than or equal to 0.05 was considered statistically significant.

Results

195 patients were enrolled for this trial, 15 patients were excluded (five patients were aged over 65 years and 10 patients declined to participate in the trial). 23 patients were excluded from analysis (11 patients conversed to open laparotomy due to uncontrollable hemorrhage, 12 patients suffered distant metastases). 157 patients completed the study (77 in the

Remi group and 80 in the OS group). Baseline patient characteristics, preoperative variables and type of surgical procedure were comparable between patients randomized for the two groups. Most patients in each group were males, and the median age was 55 years. The ASA classification for all patients was grade I to III. Concomitant diseases (such as hypertension and diabetes mellitus) were less than 30% and the median preoperative PSQI was 6 in both groups (Table 1 and Figure 1).

Pain Score and Rescue Analgesia

The NRS pain score in PACU and the proportion of PACU rescue analgesia in the Remi group was significantly higher than that in the OS group {Remi vs OS, 3 [1 to 3] vs 1 [1 to 3], $P = 0.001$; 12 (15.6%) vs 4 (5.0%), $P = 0.028$, respectively}, although there were no statistical differences in NRS pain score on POD1, POD7, and POD30 and the proportion of ward rescue analgesia within 48 h between groups was; Remi vs OS, 3 [2 to 3] vs 3 [2 to 3], $P = 0.648$; 2 [1 to 2] vs 2 [1 to 2], $P = 0.418$; 0 [1 to 1] vs 0 [1 to 1], $P = 0.656$, 45 (58.4%) vs 41 (51.3%), $P = 0.365$, respectively (Table 2).

Perioperative Outcomes

Compared with the OS group, during the similar anesthesia process, propofol consumption was significantly higher in the Remi group, the consumptions of other anaesthetics were slightly higher, though there were no statistical differences (Remi vs OS, propofol 575 [482 to 775] vs 505 [383 to 725] mg, $P = 0.020$; sevoflurane 25 [20 to 37] vs 23 [18 to 36] mL, $P = 0.229$; sufentanil 27.5 [25.0 to 30.0] vs 25.0 [25.0 to 30.0] ug, $P = 0.196$; cis-atracurium 25 [22 to 30] vs 24 [20 to 30] mg, $P = 0.364$). Extubation time was significantly prolonged in the OS group (Remi vs OS, 20 [11 to

Table 1 Baseline Patient Characteristics

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
Age, years, median [IQR]	55.0 [50.0 to 60.0]	55.0 [48.0 to 61.0]	0.876
BMI, kg/m^2, mean±SD	22.9±2.2	22.6±2.3	0.476
Male, n (%)	54 (70.1)	49 (61.3)	0.242
ASA class I/II/III, n	5/68/4	8/70/2	0.555[a]
Current smoker, n (%)	16 (20.8)	15 (18.8)	0.749
Daily drinking, n (%)	7 (9.1)	8 (10.0)	0.846
Concomitant diseases, n (%)			
Hypertension,	17 (22.1)	19 (23.8)	0.803
Diabetes mellitus	6 (7.8)	10 (12.5)	0.330
Other diseases	21 (27.3)	22 (27.5)	0.975
Preoperative vital signs			
SBP, mmHg, median [IQR]	140 [127 to 158]	138 [126 to 155]	0.545
DBP, mmHg, mean±SD	78±14	80±13	0.585
MAP, mmHg, median [IQR]	96 [88 to 108]	98 [84 to 105]	0.667
HR, bpm, median [IQR]	71 [66 to 82]	75 [67 to 86]	0.240
Type of surgical procedure, n (%)			0.839
Subtotal gastrectomy	16 (20.8)	14 (17.5)	
Hemicolectomy	28 (36.4)	30 (37.5)	
Low anterior resection	15 (19.5)	15 (18.8)	
Pancreaticoduodenectomy	8 (10.4)	6 (7.5)	
Hepatic segmentectomy	10 (13.0)	15 (18.8)	
Preoperative NRS score, median [IQR]	0 [0 to 1]	0 [0 to 1]	0.182
Preoperative PSQI, median [IQR]	6 [4 to 11]	6 [4 to 9.75]	0.827

Notes:[a] Fisher's exact test.

Abbreviations: Remi, remifentanil; OS, opioid-sparing; BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, numerical rating scale; PSQI, The Pittsburgh Sleep Quality Index.

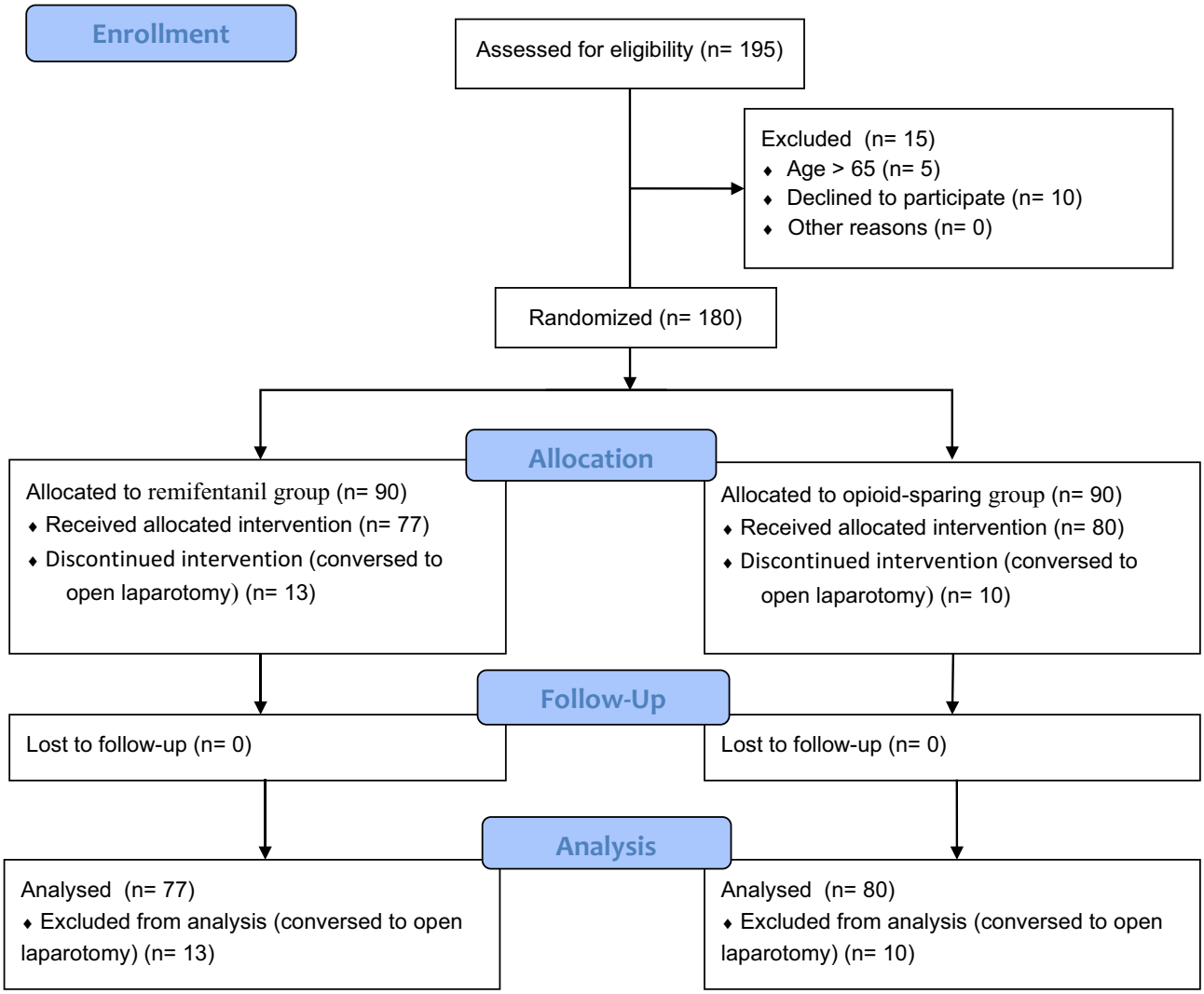

Figure 1 Trial profile. Opioid-sparing group denotes esketamine combined with dexmedetomidine group. Participants who conversed to open laparotomy were excluded from analysis.

34] vs 31 [21 to 40] min, $P < 0.01$). There was no significant difference in postoperative nausea and vomiting, surgery duration, pneumoperitoneum time, estimated blood loss, intraoperative fluid volume, and urine volume (Table 3).

Compared with the Remi group, SBP, HR and SVV were significantly lower in the OS group [Remi vs OS, SBP, 117 (95% CI, 114 to 119) vs 111 (95% CI, 108 to 114) mmHg, $P = 0.005$; HR, 65 (95% CI, 62 to 68) vs 61 (95% CI, 60 to 63) bpm, $P = 0.019$; SVV, 11 (95% CI, 9 to 12) vs 9 (95% CI, 8 to 10)%, $P = 0.031$]; other intraoperative vital signs (DBP, MAP, CO, CI and SVRI) were slightly lower than in the OS group, though there were no significant

Table 2 Pain Score and Rescue Analgesia

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
NRS pain score, median [IQR]			
PACU	3 [1 to 3]	1 [1 to 3]	0.001
POD1	3 [2 to 3]	3 [2 to 3]	0.648
POD7	2 [1 to 2]	2 [1 to 2]	0.418
POD30	0 [1 to 1]	0 [1 to 1]	0.656

(*Continued*)

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Table 2 (Continued).

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
PACU rescue analgesia, n (%)	12 (15.6)	4 (5.0)	0.028
NSAIDs	0 (0)	0 (0)	
Tramadol	12 (15.6)	3 (3.8)	
Opioids	0 (0)	1 (1.3)	
Ward rescue analgesia, n (%)	45 (58.4)	41 (51.3)	0.365
NSAIDs	16 (20.8)	20 (25.0)	
Tramadol	21 (27.3)	13 (16.3)	
Opioids	8 (10.4)	8 (10.0)	

Abbreviations: Remi, remifentanil; OS, opioid-sparing; NRS, numerical rating scale; PACU, postanesthesia care unit; POD, postoperative day; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 3 Perioperative Outcomes

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
Anesthesia duration, min, median [IQR]	236 [200 to 286]	235 [191 to 279]	0.442
Surgery duration, min, median [IQR]	172 [133 to 213]	164 [122 to 205]	0.349
Pneumoperitoneum duration, min, median [IQR]	123 [84 to 150]	116 [88 to 144]	0.523
Propofol, mg, median [IQR]	575 [482 to 775]	505 [383 to 725]	0.020
Sevoflurane, mL, median [IQR]	25 [20 to 37]	23 [18 to 36]	0.229
Sufentanil, ug, median [IQR]	27.5 [25.0 to 30.0]	25.0 [25.0 to 30.0]	0.196
Cis-atracurium, mg, median [IQR]	25 [22 to 30]	24 [20 to 30]	0.364
Remifentanil, mg, median [IQR]	0.86 [0.63 to 1.14]	-	-
Esketamine, mg, median [IQR]	-	18.0 [13.0 to 23.8]	-
Dexmedetomidine, μg, median [IQR]	-	72.0 [52.0 to 96.0]	-
Crystalloid, mL, median [IQR]	1000 [500 to 1000]	500 [500 to 1000]	0.960
Colloid, mL, median [IQR]	0 [0 to 500]	0 [0 to 500]	0.194
Urine volume, mL, median [IQR]	150 [100 to 200]	100 [100 to 200]	0.247
Estimated blood loss, mL, median [IQR]	30 [30 to 50]	30 [30 to 50]	0.356
Vasoconstrictor, n (%)	31 (40.3)	41 (51.3)	0.167
Atropine, n (%)	14 (18.2)	23 (28.8)	0.119
Intraoperative vital signs, EMM (95% CI)			
SBP, mmHg	117 (114 to 119)	111 (108 to 114)	0.005
DBP, mmHg	67 (65 to 69)	66 (64 to 68)	0.555
MAP, mmHg	85 (83 to 87)	82 (80 to 84)	0.070
HR, bpm	65 (62 to 68)	61 (60 to 63)	0.019
CO, l/min1	4.5 (4.3 to 4.6)	4.3 (4.2 to 4.5)	0.168
CI, l/(min.m^2)	2.9 (2.4 to 3.5)	2.7 (2.6 to 2.8)	0.414
SVV, %	11 (9 to 12)	9 (8 to 10)	0.031
SVRI, dyn.sec/cm^5.m^2	2232 (2120 to 2344)	2178 (2045 to 2312)	0.544
Nausea and vomiting, n (%)	32 (41.6)	34 (42.5)	0.905
Extubation, min, median [IQR]	20 [11 to 34]	31 [21 to 40]	<0.01
Malignant, n (%)	67 (87.0)	71 (88.8)	0.739
Days to first flatus, median [IQR]	2 [1 to 2]	2 [1 to 2]	0.589
Postoperative complications, n (%)	10 (13.0)	12 (15.0)	0.716

(*Continued*)

Table 3 (Continued).

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
Clavien–Dindo grade, n (%)			0.450[a]
0	67 (87.0)	68 (85.0)	
I	2 (2.6)	1 (1.3)	
II	5 (6.5)	10 (12.5)	
III	3 (3.9)	1 (1.3)	
IV	0 (0)	0 (0)	
V	0 (0)	0 (0)	
Postoperative hospital stay, median [IQR]	5 [6 to 8]	5 [7 to 8]	0.825

Notes: [a] Fisher's exact test.
Abbreviations: Remi, remifentanil; OS, opioid-sparing; EMM, estimated marginal mean; 95% CI, 95% confidence interval; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; SVRI, systemic vascular resistance index.

differences. However, the administration of atropine and vasoconstrictor were similar in both groups [14 (18.2%) vs 23 (28.8%), $P = 0.119$; 31 (40.3%) vs 41 (51.3%), $P = 0.167$] (Table 3).

There were no statistical differences in the incidence of malignant disease, days to first flatus, postoperative complications and length of postoperative hospital stay (Table 3).

PQRS and PSQI

The physiology score in PACU was significantly higher in the OS group and then was similar on POD7 (Remi vs OS, 27 [26 to 27] vs 27 [27 to 27], $P < 0.01$; 27 [27 to 27] vs 27 [27 to 27], $P = 0.327$). The scores for emotion, activities of daily living, cognitive and overall patient perspective were not significantly different between groups (Table 4).

Compared with the Remi group, the proportion of dreaminess was higher than that in the OS group during hospitalization [12 (15.6%) vs 34 (42.5%), $P < 0.01$]. In the OS group, the proportion of nightmare was also higher, though there was no statistical difference [5 (6.5%) vs 11 (13.8%), $P = 0.133$]. However, the PSQI on POD30 was similar between groups (8.27 ± 3.94 vs 8.37 ± 3.89, $P = 0.870$) (Table 4).

Table 4 Postoperative Quality Recovery Scale and Pittsburgh Sleep Quality Index

Variables	Remi (n = 77)	OS (n = 80)	*P*-value
Physiology, median [IQR]			
PACU	27 [26 to 27]	27 [27 to 27]	<0.01
POD7	27 [27 to 27]	27 [27 to 27]	0.327
Emotional, median [IQR]			
PACU	2 [2 to 3]	2 [2 to 2]	0.401
POD7	2 [2 to 2]	2 [2 to 2]	0.712
Activities of daily living, median [IQR]	12 [12 to 12]	12 [12 to 12]	0.282
Cognitive			
Baseline	17 [16 to 19]	17 [16 to 19]	0.983
POD7	17 [16 to 19]	17.5 [16.3 to 19]	0.626
Overall patient perspective	4 [4 to 5]	5 [4 to 5]	0.217
Dreaminess, n (%)	12 (15.6)	34 (42.5)	<0.01
Nightmare, n (%)	5 (6.5)	11 (13.8)	0.133
PSQI POD30, mean±SD	8.27±3.94	8.37±3.89	0.870

Abbreviations: Remi, remifentanil; OS, opioid-sparing; PACU, postanesthesia care unit; POD, postoperative day; PSQI, Pittsburgh Sleep Quality Index.

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Discussion

The randomized double-blind trial found that the administration of esketamine combined with dexmedetomidine during laparoscopic major abdominal surgery decreased the NRS pain scores in PACU and reduced the proportion of PACU rescue analgesia. In the OS group, the consumption of propofol was significantly lower than that in the Remi group, meanwhile, the consumption of other anaesthetics (sevoflurane, sufentanil and cis-atracurium) were also slightly lower. These results suggested that intraoperative esketamine combined with dexmedetomidine can be a safe and feasible opioid-sparing anesthesia regimen in laparoscopic major abdominal surgery.

It is undeniable that pain hypersensitivity and chronic pain caused by opioid analgesics are a major clinical challenge and may affect the tumor progression and prognosis of cancer patients. A follow-up study showed that patients receiving opioids several months after surgery had a higher risk of cancer-related death and overall death.[20,21] Moreover, those expressing higher expressions of μ-opioid receptor levels are more aggressive and associated with worse prognosis.[22] A standardized multimodal analgesic regimen was typically used to minimize the use of perioperative opioid and to decrease opioid-related adverse effects (eg, nausea, vomiting, sedation, gastrointestinal paralysis, pruritus, and respiratory depression) with the goal of improving and expediting patients' recovery after surgery.[23] Several studies showed that efforts to decrease the consumption of opioid for patients undergoing breast surgery,[24] arthroscopic knee and shoulder surgery,[25] total hip arthroplasty,[26] thoracoscopic surgery,[27] laparoscopic gynecological surgery[28] or vaginal pelvic reconstructive surgery[29] were successful and that opioid-sparing anesthesia for pain management postoperatively was feasible, but there were few studies about opioid-sparing anesthesia in laparoscopic major abdominal surgery. In some clinical trials, esketamine functioned as a longtime analgesic role and improved the prognosis of patients,[30,31] the addition of dexmedetomidine resulted in lower pain scores than analgesia alone at 24 h and 48 h postoperatively and with an improved prognosis of patients undergoing major gastrointestinal surgery in multiple aspects.[32,33] Esketamine combined with dexmedetomidine has been used for pre-medication in children, and produces more sedation but fewer side effects.[34,35] This combination was also successfully used in open spinal surgery, one of the most painful surgical procedures.[36] Postoperative pain is a continuous process, in order to reflect the overall level of pain in one month, we evaluated and recorded the postoperative NRS pain scores at four different time points. According to our results, 5% of patients in the OS group received rescue analgesia in PACU, while the proportion in the Remi group was three times higher. A brief assessment recovery tool, PQRS, showed that the higher NRS pain score in the Remi group lead to an SBP over 140 mmHg, thus lowering the physiology score in PACU. Also, the overall patient perspective was slightly higher in the OS group, it indicates that intraoperative esketamine combined with dexmedetomidine may provide better quality of postoperative recovery and then an improved PQRS questionnaire, which may be related to lower NRS pain scores. Therefore, we suppose that the esketamine combined with dexmedetomidine used intraoperatively may improve analgesia after laparoscopic major abdominal surgery.

It is be noted that dexmedetomidine may decrease the HR, CO and BP,[37,38] esketamine plays the opposite role because of its effect of sympathetic activation.[39] Although SBP and HR were significantly lower in the OS group, no more vasoconstrictor or atropine were required, which means that esketamine combined with dexmedetomidine was safe and as effective as remifentanil.

We should also recognize that alternative drugs themselves have a risk of complications, and the combination of multiple drugs greatly increases the incidence of adverse drug reactions. In this trial, a longer extubation time was observed in the OS group than that in the Remi group. Esketamine was considered to not prolong the recovery time in minimally invasive surgery, however, the laparoscopic major abdominal surgery duration was always over 2 h and the dose-dependency of esketamine needed to be paid more attention.[40] Dexmedetomidine has also caused delayed awakening, this combination may easily lead to over sedation.[41] Therefore, it is suggested that the infusion of esketamine and dexmedetomidine should stop more than 30 min before the surgery is completed.

Patients may suffer from sleep disturbances after surgery with the manifestations of polysomnography usually including sleep fragmentation, reduced duration of slow-wave sleep, and rapid eye movement sleep.[42] A randomized controlled study showed that the lower dose of esketamine infusion (0.5 μg/kg loading, 0.4 μg/kg/h infusion) was better than the higher dose (0.5 μg/kg loading, 4 μg/kg/h infusion) in combination with dexmedetomidine infusion.[12] This is

reasonable because esketamine is dose-dependent and higher doses of esketamine may result in postoperative hallucinations and nightmares.[43] In the OS group, a higher proportion of dreaminess may be caused by longtime continuous infusion of esketamine. However, the proportion of nightmares between groups were similar, the reason may be the administration of dexmedetomidine decreased the rapid eye movement sleep, thus decreased the proportion of nightmares and improve the sleep.[44] The increasing proportion of dreaminess and nightmares was only observed during hospitalization, and there was no statistical difference in the PSQI on POD30, which suggested that this combination has a short-term effect on postoperative sleep, but does not have a long-term effect on sleep.

Limitations

There are several limitations in this study. Firstly, we are considering that the range of age was narrow. In order to carry out the opioid-sparing anesthesia more comprehensively, a larger sample and multi-center trial is needed and it is crucial to involve a wider range of participants, specifically enrolling elder patients. Secondly, a short-term PSQI follow-up would not completely reflect postoperative sleep quality and a longer duration of postoperative follow-up was needed. Thirdly, we did not record other side effects postoperatively.

Conclusion

Esketamine combined with dexmedetomidine administrated during laparoscopic major abdominal surgery decreases the NRS pain scores in PACU and reduces the use of rescue analgesia. The protocol had no side effects on the PSQI, though it may prolong the extubation time and increase the proportion of dreaminess during hospitalization. Refined perioperative anesthetic management still needs to be further explored.

Data Sharing Statement

The data generated during the current study are available from the corresponding author (Min Zhong) upon reasonable request.

Ethical Approval and Patient Consent

The present study was approved by Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (ZF2022-129-01). This study was carried out in accordance with the Declaration of Helsinki and registered at https://www.chictr.org.cn/ (ID: ChiCTR2200060130). Written informed consent was obtained from each patient who agreed to participate in the study one day before surgery.

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Disclosure

The authors declare that they have no conflicts of interest.

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