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Research Article

Comparing the Effectiveness of S-Ketamine Combined with Sufentanil versus Sufentanil Alone for Postoperative Pain Management in Elderly Patients Undergoing Laparoscopic Radical Resection of Gastrointestinal Cancer: A Randomized Controlled Trial

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Background. The optimal analgesic dose of S-ketamine after laparoscopic gastrointestinal malignancy surgery remains unclear. This study aimed to evaluate the effect of S-ketamine combined with sufentanil in patient-controlled intravenous analgesia (PCIA) on postoperative pain relief in elderly patients undergoing laparoscopic surgery for gastrointestinal tumors. *Methods*. Elderly patients undergoing laparoscopic radical resection of gastrointestinal cancer were randomly assigned to one of three postoperative analgesia groups: F group received 2 ug/kg sufentanil in PCIA, LSF group received 0.5 mg/kg S-ketamine and 1.5 ug/kg sufentanil, and SF group received 1 mg/kg S-ketamine and 1 ug/kg sufentanil. The PCIA also contained 0.15 mg/kg of butorphanol and 0.02 mg/kg of ramosetron. Study drugs were administered via PCIA for 48 hours postoperatively. The primary outcome was the accumulated parecoxib sodium requirements within 48 hours after surgery. *Results*. A total of 105 patients were randomized, and 95 completed the trial (F group: $n = 32$, LSF group: $n = 32$, and SF group: $n = 31$). The cumulative consumption of parecoxib sodium within 48 hours postoperatively was lower in the SF group compared to that in the F group (median difference: −40 mg; 95% confidence interval: −40 to 0; $P = 0.0028$). The number of PCIA compressions within 48 hours after surgery was smaller in the SF group compared to that in the F group. NRS pain scores at 6 h and 12 h postoperatively were reduced in the SF group compared to that in the F group, both at rest and during movement. Compared to the F group, the incidence of postoperative mild depression was lower, the time to first flatus and time to first defecation were shorter, and the incidence of postoperative vomiting was lower in the SF group. The mechanical pain threshold, hyperalgesia area, and sedation scores were similar between the SF and F groups. No differences were observed in the abovementioned parameters between the LSF group and the F group. *Conclusion*. This trial demonstrated that 1.0 mg/kg S-ketamine combined with 1 ug/kg sufentanil in PCA decreased cumulative parecoxib sodium consumption within 48 hours after laparoscopic radical resection of gastrointestinal cancer in elderly patients.

1. Introduction

Inadequate postoperative pain management is a common risk factor for postoperative complications and chronic pain, leading to increased patients' distress, reduced satisfaction, and higher medical costs. Opioids are currently the most commonly used drugs for postoperative analgesia, providing substantial benefits to patients [1]. However, growing concerns about adverse effects (e.g., respiratory depression, nausea, vomiting, intestinal obstruction, and hyperalgesia)

and addiction associated with opioid use have prompted the search for alternative analgesic strategies [2, 3].

Multimodal analgesia combines two or more analgesic methods to achieve additive or synergistic analgesic effects through different pain signaling pathways [4]. It has been reported to optimize pain management while minimizing opioid-related adverse effects [5]. Patient-controlled intravenous analgesia (PCIA), compared to conventional routes of administration (i.e., oral, subcutaneous, or intramuscular), provides more effective pain relief and higher patient satisfaction.

Ketamine is an N-methyl-d-aspartate receptor inhibitor that reduces central sensitization, which is associated with hyperalgesia, opioid tolerance, and chronic pain [6]. It has emerged as a reasonable option for perioperative pain management, and a review article had reported that combining ketamine with opioids in PCIA after surgery improves analgesia and reduces opioid use [7]. S-ketamine is the optical isomer of ketamine, exhibiting faster elimination, quicker recovery, fewer nervous system side effects, and reduced respiratory secretions [8]. S-ketamine is currently used for postoperative analgesia; however, data on the optimal dosage for elderly patients undergoing laparoscopic surgery for gastrointestinal malignancies remain limited.

This clinical trial aimed to determine whether the combination of S-ketamine and sufentanil in PCIA would reduce the analgesic needs and pain scores for elderly patients undergoing laparoscopic radical resection of gastrointestinal tumors. Therefore, we examined the primary hypothesis that the combination of S-ketamine and sufentanil in PCIA reduces the accumulated parecoxib sodium requirement within 48 hours after surgery compared to sufentanil PCIA alone. Secondary outcome measures included parecoxib sodium requirements and the number of PCIA compressions at 0–6, 6–12, 12–24, and 24–48 hours after surgery, pain scores, sedation scores, postoperative depression, postoperative hyperalgesia, time to recovery of gastrointestinal function, and any potential complications associated with sufentanil or S-ketamine administration.

2. Methods

2.1. Ethics and Registration. This triple-blind, randomized, and controlled single-center clinical trial was registered at the Chinese Trial Registry (ChiCTR2100050432) on 27 August 2021, and was approved by the Ethics Committee of Nanchong Central Hospital, China (2021 (099)). It was conducted at Nanchong Central Hospital, the Second Clinical Medical Institution of North Sichuan Medical College, between September 2021 and February 2022 in accordance with the Declaration of Helsinki and the principles of the International Conference on Harmonization of Good Clinical Practice. Written informed consent was obtained from all participants before enrollment.

2.2. Patients. The eligibility criteria for elderly patients, aged between 60 and 75 years, with an American Society of Anesthesiologists (ASA) physical status of I-III, a body mass index (BMI) of less than 30 kg/m^2, and scheduled for elective laparoscopic radical resection of gastrointestinal malignant tumors, were assessed. The exclusion criteria were inability or refusal to provide informed consent, anticipated transport to the intensive care unit (ICU) after surgery, a history of cerebrovascular accident, myocardial infarction, or unstable angina within the previous 3 months, increased intracranial or intraocular pressure, a history of depressive or psychiatric disorders, chronic pain or therapy with opioids before surgery, poorly controlled or untreated hypertension (i.e., systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg), severe hepatic or kidney dysfunction, allergy to any of the study medication, alcohol or drug abuse, and participation in another study within the previous 30 days. The predefined dropout criteria included conversion from laparoscopic to a laparotomy approach and unscheduled postoperative admission to the ICU.

2.3. Randomization and Blinding. Patients were randomized to one of the three groups at a ratio of 1 : 1 : 1 to receive PCIA of low-dose of S-ketamine + sufentanil (LSF group), S-ketamine + sufentanil (SF group), or sufentanil (F group) according to a computer-generated block randomization technique (https://www.randomization.com) with a block size of six. Group allocation was concealed using sealed, opaque, and consecutively numbered envelopes. On the day of surgery, a nurse not involved in the study was given the envelope containing the randomization sequence, and she or he prepared the PCIA accordingly and labeling it as "study drug" with the serial number on the PCIA devices (TR-5-100; Tuoren, China).

All patients, nurses, outcome assessors, and physicians participating in the study were blinded to the patient grouping. The statisticians remained blind until the completion of the statistical analysis.

The PCIA included 0.5 mg/kg of S-ketamine (Hengrui Pharmaceutical Co., Jiangsu, China) + 1.5 ug/kg sufentanil + 0.15 mg/kg butorphanol + 0.02 mg/kg ramosetron in the LSF group; 1 mg/kg of S-ketamine + 1 ug/kg sufentanil + 0.15 mg/kg butorphanol + 0.02 mg/kg ramosetron in the SF group; and 2 ug/kg sufentanil + 0.15 mg/kg butorphanol + 0.02 mg/kg ramosetron in the F group. All drugs were diluted with 0.9% NaCl to a total volume of 100 mL.

2.4. Study Procedure. On the day before surgery, an outcome assessor instructed patients on the use of a 0–10 numerical rating scale (NRS: 0 indicated no pain, 10 indicated severe pain, 0–3: mild pain, 4–6: moderate pain, and 7–10: severe pain) and the PCIA devices. Additionally, a skin mechanical pain threshold test was performed using the von Frey system (IITC, Life Science, USA). Briefly, the intended incision site (periumbilical area) and the skin of the right forearm were fully exposed, and the needle of the pain meter was used to apply pressure to the umbilicus and the ulnar side of the right forearm near the cubital fossa. When the patient complained of pain, the value of the pain meter was recorded

as the patient's basal pain threshold. Each site was measured three times, and the average value was taken for analysis.

All patients underwent a routine fasting for 6–8 hours and were not allowed to access any solution or fluid 2–4 hour before the surgery. After the patients entered the operating room, an electrocardiogram, pulse oxygen saturation, invasive arterial blood pressure, and bispectral index (BIS) monitoring were performed. A right internal jugular vein access was then established. The anesthesia induction regimen consisted of midazolam 0.05 mg/kg, propofol 1 mg/kg, etomidate 0.15 mg/kg, sufentanil 0.4 ug/kg, and cisatracurium 0.15 mg/kg. After tracheal intubation, anesthesia was maintained with 1-2% sevoflurane to achieve a target of BIS between 40 and 60. Analgesia was achieved by administered 0.1–0.3 ug/kg/min of remifentanil and adjusted as appropriate. An additional sufentanil 0.15 ug/kg was given before skin incision, and cisatracurium 3 mg was added at 40 minutes intervals. Double antiemetics, dexamethasone 5 mg, and tropisetron 5 mg, were given prophylactically at the beginning of the procedure. Sufentanil 5 ug was given intravenously about 30 minutes before the end of surgery. After that, PCIA infusion was started at a rate of 2 mL/h for 48 hours, with a demand bolus of 0.5 mL and a 15 minutes lock-out time. At the end of surgery, all anesthetic drugs were discontinued, and the patients were transferred to a postanesthesia care unit (PACU) and then returned to the ward after being awake and extubated.

2.5. Data Collection. Patients were assessed for pain at rest and during movement by the outcome assessor in the PACU and surgical ward at 1, 2, 6, 12, 24, and 48 hours postoperatively. If the NRS score was greater than 4, a single bolus of 40 mg of parecoxib sodium (Dynastat, Pfizer, USA) was administered for pain relief, and the details of the use of parecoxib sodium were recorded in the doctor's order. Immediately before assessing pain severity, sedation was evaluated using a 6-point Ramsay Sedation Scale (RSS), which ranges from complete agitation to no response to pain: a score of 1 indicates insufficient sedation, 2–4 suggests satisfactory sedation, and 5-6 represents excessive sedation. Concurrently, the number of PCIA compressions in the corresponding time period was recorded.

At 48 hours after the operation, patients were tested for hyperalgesia and assessed for depression. The hyperalgesia area, based on the above-described method for measuring mechanical pain threshold, was measured by applying 30 g pressure, starting around 5 cm away from the umbilicus center along horizontal and vertical lines. The pressure was moved 0.5 cm inward until the patient reported pain, and the distance from the point to the umbilicus center was recorded. The average distance (L) of the four diameters was calculated, with the area of hyperalgesia which was defined as $4\,L^2$. Depression disorder was assessed using the Self-Rating Depression Scale (SDS), depression screening scale, where scores <50 points indicated no depression, 50–59 points indicated mild depression, 60–69 points indicated moderate depression, and scores ≥70 points indicated severe depression.

The presence or absence of nausea and vomiting, pruritus, respiratory depression, dreaminess, hallucinations, and diplopia were documented. Additionally, the time from the end of the operation to the first anal flatus and defecation was accurately recorded in hours.

2.6. Sample Size Calculation. We determined that a 30% reduction in analgesic consumption would be clinically significant. Based on the mean and standard deviation of analgesic consumption derived from the preexperimental data, the analysis using PASS version 20 with a statistical power of 80% and a two-tailed type I error of 5% yielded a group sample size of 31 patients. Considering a potential 10% dropout or protocol breach rate, 35 patients were recruited for each group.

2.7. Statistical Analysis. Statistical analysis was conducted using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Normality was evaluated using the Kolmogorov–Smirnov test before analysis. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed or as medians (25^{th}–75^{th} interquartile ranges) if not. Differences between the intervention groups and the F group were compared using the independent Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were expressed as numbers (percentage) or proportions, with differences between the intervention groups and the F group assessed using the chi-square test or Fisher's exact test as appropriate. The median difference and its 97.5% confidence intervals (CI) were calculated using the Hodges–Lehman method. Data comparisons were made between groups at each time point only. For each hypothesis testing, a two-tailed P value of less than 0.05 was considered statistically significant. For multiple comparisons or multiple testing within a hypothesis, the Bonferroni correction was applied, that is, setting the significance criterion at 0.05 divided by the number of comparisons.

3. Results

The patient recruitment process throughout the trial is shown in Figure 1. A total of 95 patients were included in the analysis, comprising 32 patients in the F group, 32 patients in the LSF group, and 31 patients in the SF group. The demographic information, ASA physical status, surgical characteristics, intraoperative opioid consumption, and preoperative mechanical pain thresholds were similar among the three groups of patients (Table 1).

3.1. Postoperative Parecoxib Sodium Consumption. As shown in Table 2, the cumulative 48-hour postoperative parecoxib sodium consumption was significantly reduced in patients in the SF group (40 (0 to 40) mg *vs.* 60 (40 to 120) mg, $p = 0.0028$) and similar for those in the LSF group (60 (40 to 80) mg *vs.* 60 (40 to 120) mg, $p = 0.8625$) as compared to

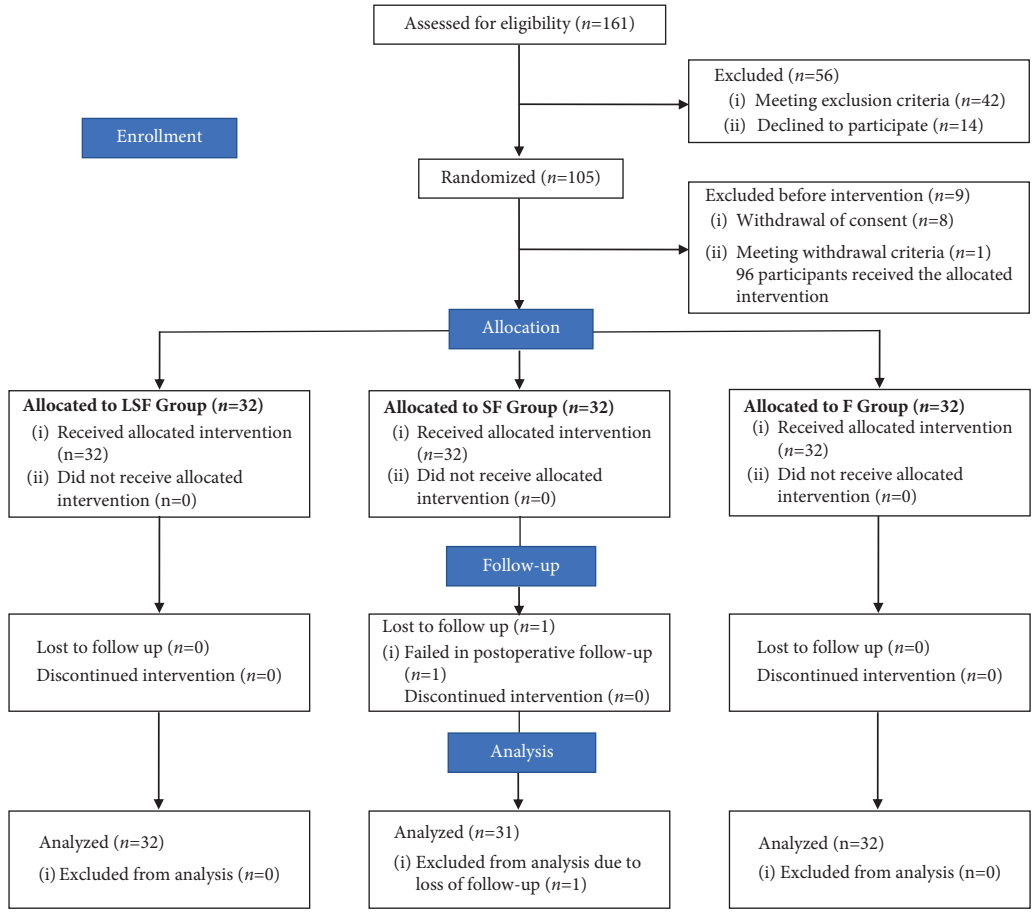

Figure 1: Patient flowchart.

Table 1: Patient characteristics.

	F group ($n = 32$)	LSF group ($n = 32$)	SF group ($n = 31$)
Age (yr)	62.0 [60.0, 72.5]	60.0 [60.0, 74.5]	67.0 [61.0, 73.0]
Male, *n* (%)	18 (56.2)	15 (46.9)	15 (48.4)
Weight (kg)	59.0 ± 10.6	56.6 ± 12.5	61.7 ± 11.5
Height (cm)	160.0 [152.5, 163.5]	160.0 [152.0, 162.0]	160.0 [153.0, 167.5]
ASA physical status, *n* (%)			
II	26 (81.3)	28 (87.5)	27 (87.1)
III	6 (18.7)	4 (12.5)	4 (12.9)
Operative site, *n* (%)			
Stomach	6 (18.8)	9 (28.1)	9 (29.0)
Colon	13 (40.6)	9 (28.1)	8 (25.8)
Rectum	13 (40.6)	14 (43.8)	14 (45.2)
Duration of surgery (min)	168.9 ± 20.1	159.3 ± 23.1	162.3 ± 21.0
Fluid volume during anesthesia (L)	2.5 ± 0.7	2.5 ± 0.6	2.3 ± 0.7
Sufentanil consumption (ug)	35.0 ± 10.5	36.5 ± 6.9	32.8 ± 9.9
Remifentanil consumption (ug)	815.6 ± 127.1	859.9 ± 145.8	871.6 ± 100.5
Preoperative mechanical pain threshold (g)			
Medial forearm	85 ± 13	88 ± 11	86 ± 12
Periumbilical area	89 ± 11	82 ± 15	84 ± 14

Data are presented as mean ± SD, median (25^{th}–75^{th} interquartile range), or number of patients (%).

that in the F group. Additionally, patients in the SF group requested fewer doses of parecoxib sodium within the initial 0–6 hours after surgery compared to that in the F group ($p = 0.0020$). Nevertheless, there were no differences in parecoxib sodium requirements between the SF and F groups during the 6–12 h, 12–24 h, and 24–48 h ($p = 0.0267$, $p = 0.0283$, and $p = 0.3289$, respectively) postoperative periods.

Table 2: Postoperative parecoxib sodium consumption and PCIA compressions.

	F group ($n = 32$)	LSF group ($n = 32$)	SF group ($n = 31$)	Differences (97.5% CI) (P value), LSF group vs F group	Differences (97.5% CI) (P value), SF group vs F group
Parecoxib sodium consumption after surgery (mg)					
48 h parecoxib sodium	60 [40, 120]	60 [40, 80]	40 [0, 40]	0 (−40, 40) [0.8625]	−40 (−40, 0) [0.0028]**
0 to 6 h	60 [40, 110]	40 [40, 80]	40 [0, 40]	0 (−40, 40) [0.7174]	−40 (−40, 0) [0.0020]**
6 to 12 h	0 [0, 40]	0 [0, 40]	0 [0, 0]	0 (0, 0) [0.4330]	0 (0, 0) [0.0267]
12 to 24 h	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 (0, 0) [0.3291]	0 (0, 0) [0.0283]
24 to 48 h	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 (0, 0) [0.7003]	0 (0, 0) [0.3289]
Number of PCIA compression after surgery (times)					
48 h PCIA compression	8 [7.25, 9]	7 [6, 9.75]	5 [4, 7]	−1 (−2, 0) [0.1153]	−3 (−4, −2) [<0.0001]**
0 to 6 h	5 [3, 5]	4 [3, 5]	3 [2, 4]	0 (−1, 1) [0.4847]	−1 (−2, 0) [0.0032]**
6 to 12 h	2 [2, 3]	2 [1, 2]	1 [1, 2]	0 (−1, 0) [0.1463]	−1 (−1, 0) [0.0009]**
12 to 24 h	1 [0, 2]	1 [0, 1]	1 [0, 1]	0 (−1, 0) [0.6218]	0 (−1, 0) [0.0673]
24 to 48 h	1 [0, 1]	0.5 [0, 1]	0 [0, 1]	0 (0, 0) [0.6567]	0 (−1, 0) [0.0743]

Data are represented as median (25^{th}–75^{th} interquartile range) and media difference (97.5% CI). The Mann–Whitney U test was employed to compare intervention groups to the F group. Following Bonferroni correction, significance thresholds (P values) were set at 0.03 for comparisons within the first 48 hours after surgery and 0.00625 for comparisons at each postoperative time point. **$P < 0.006$ in comparison to the F group.

3.2. PCIA Compression times. Within the first 48 h after surgery, the number of PICA compressions was lower in the SF group ($p < 0.0001$) and similar in the LSF group ($p = 0.1153$) compared with that in the F group. The data further showed that the number of PCIA presses in the SF group was significantly fewer than that in the F group at 0–6 h and 6–12 h after surgery ($p = 0.0032$ and $p = 0.0009$, respectively). However, no differences were observed in the number of PCIA presses during the 12–24 h and 24–48 h postoperative periods between the SF and F groups ($p = 0.0673$ and $p = 0.0743$, respectively) (Table 2).

3.3. Postoperative Sedation and Pain Scoring. No significant differences were observed in RSS scores among the three groups at 1, 2, 6, 12, and 24 h after surgery ($p > 0.05$, Figure 2(a)). Sedation scores ranged between 2 and 5 across all postoperative assessment times, indicating well-maintained sedation status in each group of patients.

In comparison to the F group, the SF group exhibited significantly lower resting NRS scores at 6 h and 12 h after surgery ($p = 0.0012$ and $p = 0.0014$, respectively), with no differences at other time points ($p > 0.05$). No significant differences were found between the LSF and the F groups in resting NRS scores at any follow-up time point ($p > 0.05$) (Figure 2(b)). Moreover, the SF group displayed significantly lower movement NRS scores at 6 h and 12 h after surgery compared to that in the F group (both $p < 0.0001$), with no differences at any other time point ($p > 0.05$). Additionally, no significant differences were observed between the LSF and the F groups in movement NRS scores at any follow-up time points ($p > 0.05$) (Figure 2(c)). These findings indicate that the SF group experienced reduced pain in both resting and movement states during the early postoperative period.

3.4. Postoperative Mechanic Pain Thresholds and Hyperalgesia. Mechanical pain thresholds and hyperalgesia were evaluated 48 hours after surgery. No significant differences were observed in the mechanical pain thresholds of the medial forearm and incision areas between the LSF group and SF group when compared to that in the F group ($p > 0.05$). Similarly, no significant differences were detected in the hyperalgesia area surrounding the incision between the LSF group and SF group when compared to that in the F group ($p > 0.05$) (Table 3).

3.5. Postoperative Depression Levels. The number of patients classified as having mild depression by the SDS screening scale was 8 in the F group, 9 in the LSF group, and 1 in the SF group. Compared with the F group, the incidence of postoperative depression was lower in the SF group ($p = 0.014$) and similar in the LSF group ($p = 0.777$) (Table 3).

3.6. Recovery Time of Gastrointestinal Function. Both the time to first anal exhaustion and the time to first defecation were shorter for patients in the SF group compared to those in the F group (both $p < 0.0001$). However, there were no significant differences in the time to first anal exhaustion and the time to first defecation between the LSF and F groups ($p = 0.5755$ and $p = 0.3020$, respectively). These findings indicate that postoperative gastrointestinal function significantly improved in patients treated with 1.0 mg/kg of S-ketamine combined with sufentanil PCIA (Table 3).

3.7. Adverse Events. During the 48-hour postoperative observation period, the incidence of postoperative vomiting was significantly lower in the SF group than in the F group ($p = 0.022$). Itching occurred in one patient each in both the F and LSF groups. Vivid dreams were experienced by three patients in the F group, three patients in the LSF group, and four patients in the SF group. One patient in the SF group reported hallucinations. There was one case of diplopia in both the F and SF groups. No respiratory depression was reported in any patient group. There were no significant

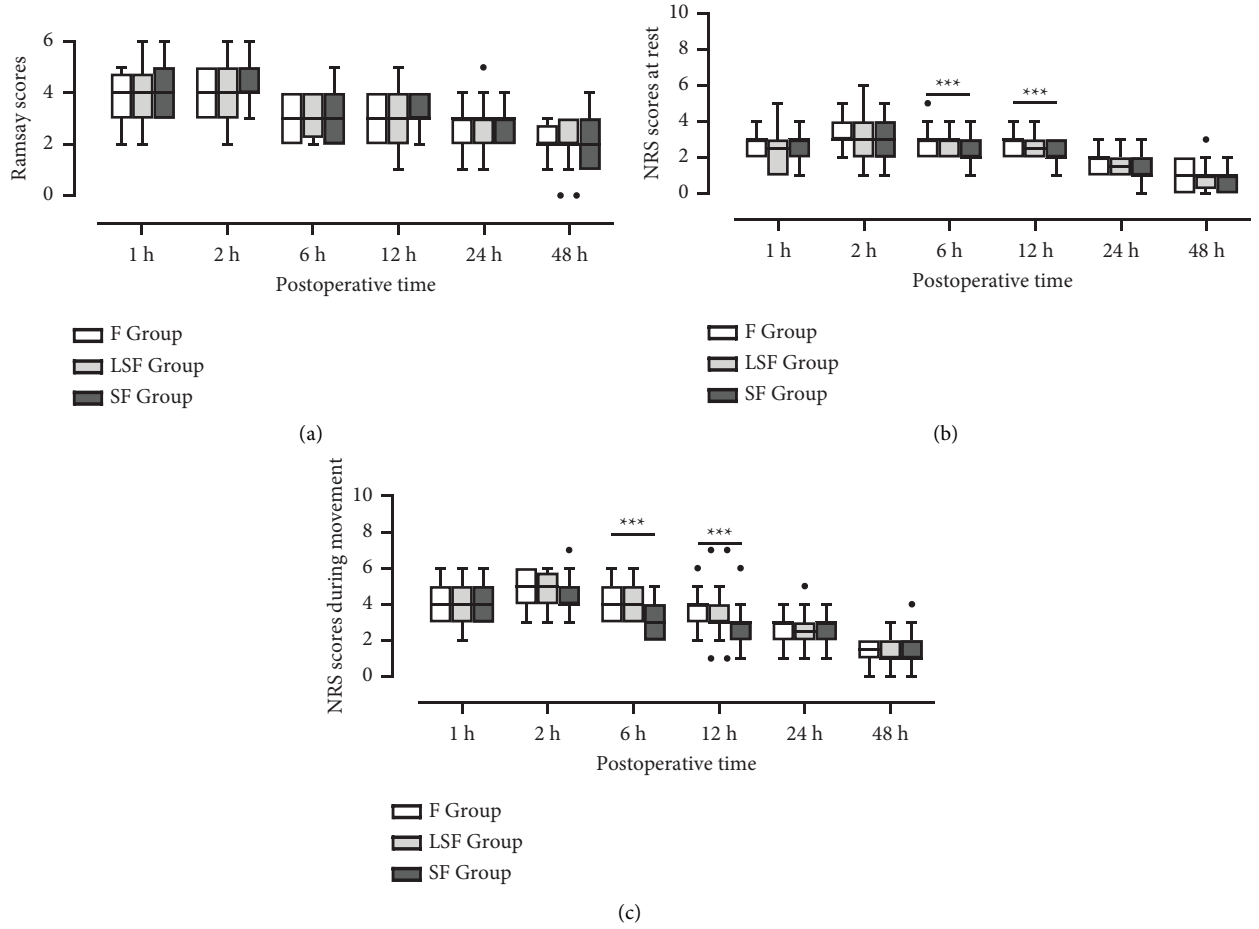

Figure 2: Comparison of postoperative RSS scores and NRS scores of the three groups of patients at different time points. (a) RSS scores; (b, c) NRS scores for resting and movement states, respectively. Data are shown as box-and-whisker plots following the Tukey style and analyzed using the Mann–Whitney U test. After Bonferroni correction, the criterion for significance was 0.004 for each postoperative time point. $^{***}P < 0.004$ in comparison to the F group.

differences in the incidence of itching, vivid dreams, hallucinations, and diplopia between the SF and LSF groups compared to that in the F group ($p > 0.05$) (Table 3).

4. Discussion

In this triple-blind randomized controlled trial, we found that patients in the SF group who received PCIA with 1.0 mg/kg of S-ketamine combined with 1 μg/kg sufentanil had a lower demand for parecoxib sodium within 48 h after surgery compared to those receiving 2 μg/kg sufentanil PCIA in the F group. Furthermore, these SF group patients had fewer PCIA compressions within 48 h and lower pain scores (at rest or during movement) at 6 h and 12 h postoperatively. Additionally, the SF group patients exhibited a reduced incidence of postoperative depression, a lower occurrence of vomiting, and an earlier recovery of gastrointestinal function. However, the use of 0.5 mg/kg of S-ketamine combined with 1.5 μg/kg sufentanil PCIA in the LSF group did not demonstrate similar advantages.

Currently, laparoscopic surgery is the preferred approach for the radical treatment of gastrointestinal cancer due to its smaller incision compared to traditional open surgery [9]. However, postoperative pain still persists, with some cases reporting severe pain following laparoscopic procedures [10]. Adequate postoperative analgesia is crucial in promoting early recovery of gastrointestinal function, reducing the occurrence of lower limb thrombosis and pulmonary embolism and decreasing surgical complications and mortality, as well as enabling patients to get out of bed and move early [11]. In this study, we selected parecoxib sodium as the rescue medication for postoperative analgesia, which has been reported to effectively alleviate pain and exhibit an opioid-sparing effect following gastrointestinal surgery [12].

It is currently advocated to reduce the use of perioperative opioids due to the potential side effects of opioids, such as postoperative nausea and vomiting and intestinal paralysis [13–15]. Numerous studies have shown the potential of S-ketamine for postoperative analgesia to reduce the use of opioids [16–19]. In these studies, S-ketamine is typically administered during surgery and continues until 12–48 hours postoperatively or as an adjuvant added to the PCIA. Bornemann-Cimenti et al. [16] confirmed that S-

Table 3: Postoperative characteristics and side effects.

	F group ($n = 32$)	LSF group ($n = 32$)	SF group ($n = 31$)	Differences (97.5% CI) (P value), LSF group vs F group	Differences (97.5% CI) (P value), SF group vs F group
Postoperative mechanical pain threshold (g)					
Medial forearm	71.1 ± 17.3	72.9 ± 13.1	75.8 ± 11.2	1.78 (−6.72, 10.28) [0.6433]	4.71 (−3.46, 12.89) [0.2049]
Periumbilical area	69.3 ± 20.2	74.0 ± 20.0	74.9 ± 20.9	6 (−6, 16) [0.3137]	7 (−6, 17) [0.2536]
Hyperalgesia area (cm^2)	41.2 ± 9.1	38.2 ± 11.0	36.2 ± 9.4	−2.97 (−8.58, 2.64) [0.2441]	−4.93 (−10.11, 0.25) [0.0386]
Postoperative depression, n (%)					
No depression	24 (75.0)	23 (71.9)	30 (96.8)	−0.03 (−0.18, 0.12) [0.777]	−0.22 (−0.35, −0.08) [0.014]*
Mild depression	8 (25.0)	9 (28.1)	1 (3.2)		
Time to first flatus (h)	40.5 [36.25, 49]	39.5 [38, 52.75]	24 [23, 36]	1 (−3, 5) [0.5755]	−14 (−18, −10) [<0.0001]***
Time to first defecation (h)	82.7 ± 12.6	79.0 ± 15.8	55.2 ± 10.2	−3.72 (−11.65, 4.22) [0.3020]	−27.53 (−33.94, −21.11) [<0.0001]***
Adverse reactions, n (%)					
Vomiting	5 (15.6)	3 (9.4)	2 (6.4)	−0.06 (−0.18, 0.05) [0.450]	−0.09 (−0.21, 0.02) [0.022]*
Itching	1 (3.1)	1 (3.1)	0	0 (−0.08, 0.08) [1]	−0.03 (−0.10, 0.04) [1]
Dreaminess	3 (9.4)	3 (9.4)	4 (12.9)	0 (−0.12, 0.12) [1]	0.04 (−0.08, 0.15) [0.708]
Hallucinations	0 (0)	0 (0)	1 (3.2)	—	[0.492]
Diplopia	1 (3.1)	0 (0)	1 (3.2)	[1]	[1]

Data are represented as mean ± SD, median (25th–75th interquartile range), number of patients (%), and media difference (97.5% CI). The independent Student's t-test, Mann–Whitney U test, chi-square test, or Fisher's exact test was employed to compare the intervention groups to the F group, as appropriate. Following Bonferroni correction, the threshold for significance was set at 0.03. $^{*}P < 0.03$ and $^{***}P < 0.004$ in comparison to the F group.

ketamine has obvious advantages in reducing postoperative opioid consumption and hyperalgesia at the incision site after laparotomy. Kadic et al. [17] demonstrated that a single intravenous bolus of 5 mg/ml S-ketamine after anesthesia induction, followed by a continuous infusion of 2 ml/h for 24 h, in combination with oral pregabalin, significantly reduced opioid consumption. Prophylactic use of S-ketamine is considered to have an antihyperalgesic effect after cesarean section [18]. Adding S-ketamine to PCIA reduced the cumulative consumption of oxycodone within 24 hours after major lumbar fusion surgery without additional side effects [19]. Our study provides further evidence that 1 mg/kg of ketamine combined with sufentanil for postoperative analgesia (PCIA) can reduce the consumption of parecoxib sodium within 48 hours after laparoscopic radical resection of gastrointestinal cancer in elderly patients. However, some studies have also reported that small doses of S-ketamine applied during surgery have no significant advantage in postoperative analgesia. For example, Brinck et al. [20] reported that, compared to a placebo, intraoperative use of S-ketamine had no effect on the opioid consumption after spinal surgery. Becke et al. [21] also found that in pediatric urological surgery, using S-ketamine did not show a significant advantage over a placebo in reducing opioid usage and side effects. In the abovementioned two studies, S-ketamine was mainly administered during the surgical period. Therefore, we speculate that the postoperative analgesic effect of S-ketamine may vary depending on the dosage, duration of administration, and type of surgery.

In our study of patients receiving PCIA multimodal analgesia, we observed that pain was most intense during the first 12 h postoperatively, gradually subsided after 24 h, and greatly alleviated by 48 h (with the lowest NRS scores). Under equivalent sedation levels, the NRS scores of patients in the SF group were markedly lower than those in the F group at 6 h and 12 h postoperative periods, regardless of whether at rest or with movement. Meanwhile, the number of the PCIA compressions decreased during the 0–6 h and 6–12 h postoperatively, and the demand for parecoxib sodium within 0–6 hours was also significantly reduced. We can speculate that the lower consumption of parecoxib sodium in the SF group within 48 hours might be mainly attributed to the reduced pain scores during the first 12 h after surgery, which, in turn, could be due to the combined use of 1 mg/kg S-ketamine and 1 μg/kg sufentanil in the PCIA. In other words, the combined use of S-ketamine and sufentanil provides patients with superior postoperative analgesia than sufentanil alone.

Hyperalgesia, a condition associated with chronic persistent pain, is considered a consequence of central sensitization and plasticity [22]. Remifentanil is a known opioid that can cause postoperative hyperalgesia [23]. In the current study, we did not detect significant differences in mechanical pain threshold and hyperalgesia areas around the incision among groups of patients. This may be due to the small dose of remifentanil used in this study and the addition of butorphanol in the PCIA, which helps alleviate opioids-induced hyperalgesia [24].

Postoperative depression, exhibiting an increasing trend among the elderly population, may interact with anesthesia and surgery, resulting in a significant increase in morbidity and mortality [25, 26]. S-ketamine has been reported to possess both analgesic and antidepressant properties, which could potentially benefit patients experiencing postoperative depression [27]. Our findings showed that the incidence of postoperative mild depression in the SF group was significantly lower than in the F group, which was consistent with the results reported by Han et al. [28]. For patients with gastrointestinal tumors, the restoration of gastrointestinal function following surgery is particularly important. Our findings demonstrated that, despite similar intraoperative fluid volume and surgery duration, the recovery time of gastrointestinal function was significantly shorter in the SF group than in the F group. This may be associated with the use of fewer opioids (sufentanil) in the PCIA for patients in the SF group. Additionally, we observed a reduced incidence of postoperative vomiting in the SF group compared to that in the F group. However, in the LSF group with a 0.5 mg/kg dose of S-ketamine and 1.5 μg/kg of sufentanil, the anticipated protective effect against postoperative vomiting was not observed.

4.1. Study Limitation. This study has several limitations. First, the main limitation is the absence of long-term data on the development of persistent postoperative pain, which is undoubtedly an important outcome parameter. Second, the sample size calculation was based on analgesic drug consumption, which may reduce the statistical power for other observational indicators. Third, the relatively short observation period for secondary outcomes, particularly postoperative hyperalgesia and postoperative depression, might introduce bias into the results. Lastly, this study was conducted in a single-center setting.

5. Conclusion

Combining 1.0 mg/kg of S-ketamine with sufentanil in the PCIA effectively reduces parecoxib sodium consumption within 48 hours after surgery for patients, compared to using sufentanil in the PCIA alone. This combination also decreases the number of PCIA compressions, lowers the incidence of postoperative vomiting and depression, and facilitates an earlier recovery of gastrointestinal function without increasing the occurrence of hyperalgesia and adverse effects. This regime can be applied to elderly patients for undergoing laparoscopic radical resection of gastrointestinal malignant tumors.

Data Availability

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ji Wang, Yu Du, Yue-Shuang Tan, Yu Liu, and Ai-ping Wen conceptualized and designed the study; Ji Wang and Yue-Shuang Tan collected the data; Yu Du and Yu Liu analyzed the data; Ji Wang, Yu Du, and Yue-Shuang Tan drafted the manuscript; Ji Wang and Ai-ping Wen did critical review of the manuscript; and Ji Wang, Yu Du, Yue-Shuang Tan, Yu Liu, and Ai-ping Wen did final edit. All authors read and approved the final manuscript. Ji Wang, Yu Du, and Yue-Shuang Tan contributed equally to this study.

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