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Effect of combination of remimazolam and sevoflurane on elderly patients' recovery quality from general anesthesia after laparoscopic abdominal surgery: a randomized controlled trial

Xiawei Lai[1,3†], Shuxian Liu[2,4†], Di Wang[2,4], Yuqing Chi[2,3], Xiaoqun Su[2,3], Lideng Guo[2,5], Zhijing Zhang[2,6*] and Haihui Xie[2,6*]

Abstract

Purpose Remimazolam toluene sulfonic acid is a short-acting benzodiazepine primarily studied for intravenous anesthesia. To date, few studies have focused on the effects of the combination of remimazolam and inhalation anesthesia or its impact on postoperative recovery. Our study aims to investigate the influence of remimazolam combined with sevoflurane for general anesthesia maintenance on postoperative recovery quality in elderly patients undergoing laparoscopic abdominal surgery.

Methods A total of 109 patients, aged 60 to 80 years old, scheduled for laparoscopic gallbladder or hernia surgery were randomly divided into two groups: remimazolam group (Group R) and remimazolam-sevoflurane combination group (Group S). Group R had remimazolam for anesthesia maintenance, while Group S received remimazolam and sevoflurane. Both groups followed the same induction protocol, with bispectral index (BIS) maintained between 40 and 60 during surgery. The primary outcome was assessed with the Quality of Recovery (QoR)-15 score. The secondary outcomes included loss of consciousness (LoC), perioperative hemodynamic variables, extubation time, and the incidence of postoperative adverse events. During the study, 7 patients were lost to follow-up, and finally, 102 patients were included in the statistical analysis. The data will be analyzed in a modified full analysis set.

Results Group S had higher QoR-15 and physical comfort scores on postoperative day (POD) 1 and POD3 compared to Group R (135.0[8.0] vs. 132.0[11.0], $P=0.004$; 143.0[6.0] vs. 141.0[7.0], $P=0.007$). Despite using less remifentanil ($P=0.021$), Group S had a significantly longer extubation time ($P=0.048$). There were no significant differences in induction time, perioperative hemodynamic variables, or postoperative adverse events between the groups.

†Xiawei Lai and Shuxian Liu contributed equally to this work.

*Correspondence:
Zhijing Zhang
jingamigo@163.com
Haihui Xie
xhh900@163.com
Full list of author information is available at the end of the article

Conclusion Combining remimazolam with sevoflurane improves postoperative recovery quality in elderly patients undergoing laparoscopic abdominal surgery. This approach ensures optimal anesthesia depth and sedation while minimizing adverse events and complications.

Trial registration Chinese Clinical Trial Registry ChiCTR2200065332. Date of registration: 02/11/2022.

Keywords Remimazolam, Sevoflurane, Quality of recovery, Elderly

Introduction

The rollout of Enhanced Recovery After Surgery (ERAS) has allowed patients to play a more active role as key decision-makers in the rehabilitation process. This "patient-centered" transition (Mithany et al. 2023; Taurchini et al. 2018) not only improves patient satisfaction and engagement but also enhances the overall effectiveness and quality of the recovery. QoR score serves as an objective assessment of overall health following patient-centered anesthesia and surgery. In 2013, Stark et al. (2013) selected the 15 strongest psychometrically performing items from each dimension of the QoR-40 to create the QoR-15, for patients' physical and mental well-being evaluation. The QoR-15 features high time efficiency, responsiveness, and high completion rate, and has been extensively adopted in clinical research nationally and internationally (Myles et al. 2022).

As the global population ages (Affairs. UNDoEaS. 2023) and more elderly people undergo surgery, ensuring surgical safety has become a critical public health concern worldwide. Elderly patients, frequently presenting with cardiovascular and cerebrovascular conditions, are prone to severe hemodynamic fluctuations during surgery (Südfeld et al. 2017). These fluctuations can be detrimental to postoperative outcomes and overall recovery quality. Remimazolam, a novel benzodiazepine, is characterized by rapid onset of perioperative sedation, short duration, swift recovery, stable hemodynamics, no accumulation, and metabolism independent of the liver and kidneys. It also causes few adverse reactions and can be rapidly reversed by flumazenil (Jhuang et al. 2021; Tang et al. 2022). Theoretically, remimazolam could serve as an ideal adjunct for the induction and maintenance of general anesthesia in elderly patients. Nonetheless, our prior research (Fei et al. 2023) indicates that when used alone intravenously for general anesthesia maintenance in elderly patients, remimazolam may occasionally cause issues like persistent hypertension or BIS values consistently over 60—both requiring medical intervention. Sevoflurane, an inhalational anesthetic, can cause a sedative effect, relieve pain, relax muscles, lower blood pressure, and reduce inflammation. The additional use of sevoflurane throughout the surgical procedure can help mitigate the stress response, maintain vital signs, reduce the risk of intraoperative awareness and enhance patients' postoperative comfort.

To date, most clinical research on remimazolam examines its application in total intravenous anesthesia (Hu et al. 2022). The effectiveness and safety of the combination of remimazolam and inhalational anesthesia and its impact on the quality of subsequent postoperative recovery are understudied. Hence, we hypothesize that the combined use of remimazolam and sevoflurane during the maintenance of general anesthesia may stabilize hemodynamics and BIS values, facilitating improved postoperative recovery for elderly patients undergoing laparoscopic abdominal surgery.

Methods

Ethics and registration

This research is a randomized controlled clinical trial and was approved by the Ethics Committee of the Tenth Affiliated Hospital of Southern Medical University (KYKT2022-028-B2). It was registered at the Chinese Clinical Trial Registry (ChiCTR2200065332).

Recruitment

Informed consent was obtained from all participants or their family members, and consent forms were signed.

Patients who had planned to have elective laparoscopic cholecystectomy or laparoscopic hernia repair were enrolled when the following criteria were met:

1. Patients aged 60 to 80 years old.
2. Patients were assigned an American Society of Anesthesiologists (ASA) physical status classification level I to III.

The exclusion criteria are as follows:

1. Patients allergic to components of medicine such as remimazolam toluene sulfonate, and sevoflurane.
2. Patients who had used benzodiazepines or opioids within 1 month.
3. Patients with a medical history of mental disorders.
4. Patients with severe heart, lung, liver, and kidney abnormalities.
5. BMI ≥ 28 kg/m^2.

6. And patients unable to understand the written information about the trial or the informed consent form.

Randomization

In this study, the simple random method was adopted. 109 patients were divided randomly into two groups by SPSS 25.0. This study was carried out in a single-blind way. In this case, the entire trial was blind to the patients. Since using sevoflurane as the inhalation anesthetic during surgery made it impossible to keep the anesthesia providers blinded. To mitigate potential subjective bias, a third-party evaluation was implemented, ensuring that the researchers administering the drug were separate from those evaluating the trial results, thus preventing subjective influence by those aware of the patient groupings.

Interventions

Informed consent was signed 1 day before surgery and QoR score was obtained at the same time. Patients' baseline status such as electrocardiograph (ECG), heart rate (HR), pulse blood oxygen saturation (SpO_2), BIS, and mean arterial pressure (MAP) were monitored regularly before anesthesia.

After baseline vital signs and BIS were recorded, an intravenous infusion of remimazolam toluene sulfonate(trade name: Ruibeining, with a concentration of 36 mg) (6 mg/kg/h) was given to the patient, which was defined as the start of anesthesia induction. The time from the remimazolam toluene sulfonate infusion to the patient's loss of consciousness (LoC) was recorded. We defined LoC as no response from the patient to shoulder shaking (MOAA/S ≤ 1) (Table 1). After LoC confirmation, cis-atracurium (0.3 mg/kg) and sufentanil (0.2–0.4 μg/kg) were administered intravenously. During the operation, anesthesia in Group R was maintained with remimazolam (0.5–1.0 mg/kg/h), while Group S received remimazolam combined with 0.5 MAC sevoflurane, with only the dose of remimazolam (0.5–1.0 mg/kg/h) adjusted and the concentration of sevoflurane unchanged. In this way, the BIS was kept between 40 and 60. Remifentanil (0.2–0.3 μg/kg/min) and cis-atracurium (0.06–0.12 mg/kg/h) were maintained in both groups throughout the surgery, and norepinephrine, was used to keep blood pressure within 20% above or below the baseline level if necessary. Cis-atracurium and sevoflurane administration were stopped 30 min prior to the completion of surgery; sufentanil (5 μg) and ondansetron (4 mg) were injected intravenously. Remimazolam and remifentanil administration was stopped at the last suture. While waiting for the patient to recover naturally, the clinical researchers may give neostigmine or flumazenil to the patient if necessary. Hemodynamic data, BIS, and extubation time were documented at each time point during the operation. The patient was later sent to the post-anesthesia care unit (PACU) for further observation after resuscitation and extubation, and the occurrence of adverse events was recorded simultaneously. The researchers conducted bedside QoR-15 scores collection on POD1 and POD3 days after surgery.

Table 1 The Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale

Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Outcomes

The primary outcomes were the QoR-15 scores. The secondary outcomes included LoC, perioperative hemodynamic variables (HR, MAP, SpO_2) at different time points (T0: arrive at the operating room; T1: before induction; T2: 1 min after induction; T3: the beginning of surgery; T4: 15 min after the surgery; T5: 30 min after the surgery; T6: the end of surgery; T7: after extubation; T8: discharge from PACU), the extubation time, and the incidence of postoperative adverse events during anesthesia and the emergence period, such as nausea and vomiting, fluctuating blood pressure, delayed emergence and intraoperative awareness. QoR-15 is a validated questionnaire used to assess postoperative recovery in various clinical settings. The questionnaire consists of 15 questions that evaluate conditions in the five dimensions: physical independence, pain, physical comfort, psychological support, and emotional state. QoR-15 items are scored on a scale from 0 (poor recovery) to 150 (excellent recovery).

Statistical analysis

The primary outcomes of this study were the QoR-15 scores, and the sample size was calculated according to our pre-trial results. The standard deviation (σ) of the QoR-15 scores on the first postoperative day was 8.72 and the minimum clinically important difference was 6. To determine the sample size, α for two-sided tests at 0.05 and power level (1-β) to be 0.9. The PASS 25.0 software was used for data calculation and analysis. According to the results, 46 cases were required for each group. Considering a potential dropout rate of 10%, 51 cases

per group were required, totaling 102 cases for the experiment.

Quantitative variables were expressed as mean (standard deviation, SD) or median [interquartile range, IQR]. An independent-sample *t*-test was used to compare the means of Group R and Group S, and the Shapiro–Wilk test was used to examine the normal distribution of data. The Mann–Whitney *U* test would be adopted for non-normally distributed data. Categorical variable comparison between the two groups was done using the chi-square test or Fisher's exact test. Statistical analysis was performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad 8.0 (GraphPad Software, San Diego, CA, USA). All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline data

In this study, 117 patients were initially assessed for eligibility, among whom 8 were excluded. A total of 109 patients were randomly divided into two groups, with 53 patients in group R and 56 patients in group S. During the follow-up process, 7 patients met the dropout criteria due to loss to follow-up. Thus, the analysis was performed with data from 102 patients, with 51 patients in each group (Fig. 1). The baseline characteristics of the two groups (Table 2) showed no significant differences in terms of age, sex, body mass index (BMI), education level, comorbidities, surgical type, and surgical duration. Therefore, group R and group S were comparable.

The QoR-15 score for the two groups at different time points, and the scores for the five dimensions, were presented as median [IQR] (Table 3). The QoR-15 scores on the 1st and 3rd postoperative days in Group S were higher than those in Group R, showing statistically significant differences. Group S also registered a higher score in physical comfort on the 1st and 3rd days following surgery, and these differences were statistically significant. This means that when sevoflurane is used in combination with anesthesia maintenance, patients can achieve a higher quality of postoperative recovery, especially in terms of physical comfort. Preoperative QoR-15 scores and scores in five dimensions in both groups were analyzed, indicating no statistically significant differences in emotional state, psychological support, physical independence, and pain (Fig. 2).

It took 2.3(0.5) min in both groups to lose consciousness after anesthesia induction, and the difference was not statistically significant. The extubation time of patients in Group R and Group S was 25.0[17.0–42.8]

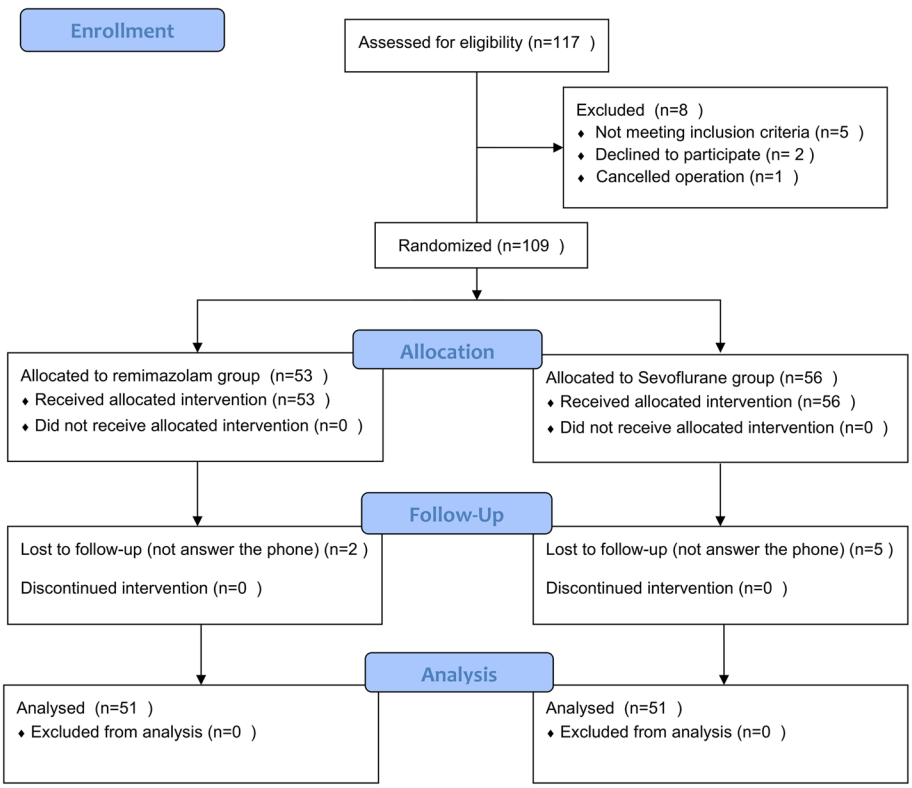

Fig. 1 CONSORT flow diagram

Table 2 Baseline patient characteristics

	Group R (*N* = 51)	Group S (*N* = 51)	*P*-value
Age (years)	69.0[7]	69.0[5]	0.749
Male, *n*(%)	42(82.4)	38(74.5)	0.336
BMI (kg/m^2)	23.3(2.6)	22.5(2.5)	0.125
Education, *n*(%)			0.961
Elementary school and below	33(64.7)	35(68.6)	
Middle school	18(35.3)	11(21.6)	
College and above	0(0)	5(9.8)	
Comorbidities, *n*(%)			
Hypertension	19(37.3)	22(43.1)	0.545
Diabetes mellitus	5(9.8)	6(11.8)	0.750
Surgical type, *n*(%)			0.826
Laparoscopic cholecystectomy	14(27.5)	15(29.4)	
Laparoscopic hernia repair	37(72.5)	36(70.6)	
Surgical time (min)	80.0[40.0]	75.0[33.0]	0.320

The values are expressed as means (SD), no. (%) or median [inter-quartile range]

BMI body mass index

min and 32.0[22.0–40.0] min respectively, and this difference was statistically significant (Table 4). This indicates that the combined use of sevoflurane for anesthesia maintenance may prolong the extubation time of patients after surgery.

Throughout the study, BIS values in both groups remained stable within the range of 40 to 60 after anesthesia induction and during maintenance. The vital signs of the two groups, including measurements of MAP, HR, and SpO_2, were similar at eight different times, with stable hemodynamics (Fig. 3). The results show that the combined use of remimazolam and sevoflurane can keep hemodynamics stable and maintain sufficient anesthesia depth, which proves the effectiveness of the combined use of the two drugs.

During the operation, the dose of remifentanil used in Group S was significantly smaller than that in Group R, and the difference was statistically significant. This result indicates that combined anesthesia drugs can reduce the dosage of opioid drugs. There was no significant difference in the dose of norepinephrine and remimazolam between the two groups (Table 5).

In terms of peri-operative adverse events, there were no statistically significant differences between Group R and Group S in the incidences of hypotension, bradycardia, PONV, delayed emergence, and anaphylactic reactions. No injection pain, hypertension, or intraoperative awareness occurred in the patients of both groups (Table 6). This indicates that the safety of remimazolam combined with sevoflurane anesthesia is similar to that of total intravenous anesthesia with remimazolam alone.

Discussion

This study demonstrated that Group S had a higher QoR-15 score on the first and third postoperative days after minor laparoscopic abdominal surgery, compared to Group R. This difference was statistically significant. Additionally, the physical comfort score of Group S was registered higher than Group R's on both the first and third days after the surgery. Patients' physical comfort may be associated with postoperative nausea and vomiting, and abdominal pain resulting from inadequate use of intraoperative muscle relaxants (Li 2019). Such abdominal pain will further impact patients' breathing, appetite, and sleep. The muscle relaxant used during the operation is mainly responsible for muscle relaxation to ensure better compliance of the abdominal muscles. However, sevoflurane may also, to some extent, help prevent inflammation and inflammation-induced tissue damage, which may contribute to shortening the peripheral nerve recovery time and improving the patient's physical comfort.

A large number of studies have centered on the application of remimazolam in anesthesia, with special emphasis on its influence on the quality of postoperative recovery in comparison to other anesthetic drugs like propofol, sevoflurane, and desflurane. When compared with the traditional sedative propofol, remimazolam typically shows either superior (Tang et al. 2023) or non-inferior (Choi et al. 2022) recovery quality scores on POD1, especially in aspects such as physical independence, psychological support, and emotional state. Moreover, remimazolam decreases the frequency of awakenings and the incidence of hypotension during

Table 3 Comparison of quality of recovery-15 scores in the two groups

	Group R	Group S	Median difference (95% CI)	*P*-value
Total QoR-15				
Preop	141.0[7.0]	143.0[6.0]	1 (−1, 3)	0.182
POD1	132.0[11.0]	135.0[8.0]	4 (1, 7)	0.004*
POD3	141.0[7.0]	143.0[6.0]	2 (1, 4)	0.007*
Emotional state				
Preop	37.0[3.0]	38.0[3.0]	0 (−1, 1)	0.749
POD1	38.0[3.0]	39.0[1.0]	1 (0, 1)	0.096
POD3	39.0[2.0]	40.0[1.0]	0 (0, 1)	0.260
Physical comfort				
Preop	46.0[4.0]	47.0[3.0]	1 (0, 1)	0.273
POD1	41.0[6.0]	44.0[5.0]	2 (1, 4)	0.001*
POD3	45.0[3.0]	47.0[3.0]	1 (0, 2)	0.004*
Psychological support				
Preop	19.0[2.0]	19.0[1.0]	0 (0, 1)	0.248
POD1	19.0[2.0]	19.0[1.0]	0 (0, 1)	0.230
POD3	19.0[2.0]	19.0[1.0]	0 (0, 1)	0.087
Physical independence				
Preop	19.0[2.0]	19.0[1.0]	0 (0, 0)	0.503
POD1	16.0[4.0]	17.0[3.0]	1 (0, 2)	0.191
POD3	18.0[2.0]	19.0[1.0]	0 (0, 1)	0.068
Pain				
Preop	20.0[1.0]	20.0[0]	0 (0, 0)	0.067
POD1	17.0[2.0]	17.0[2.0]	0 (0, 1)	0.157
POD3	19.0[1.0]	19.0[1.0]	0 (0, 0)	0.624

The values are expressed as median [inter-quartile range]

POD postoperative day, *Preop* preoperative, *QoR* quality of recovery, *CI* confidence interval

* $P < 0.05$

the first postoperative night, and it demands less pain intensity (Tang et al. 2023) and a lower amount of analgesic drugs in PACU (Choi et al. 2022). It also maintains a more stable hemodynamic condition (Mao et al. 2022) and requires the use of intraoperative vasoactive drugs less frequently. Nevertheless, remimazolam has certain limitations. It may be slightly inferior to propofol in terms of early-postoperative cognitive recovery and emotional state, especially in day-surgery cases. In such cases, remimazolam might cause postoperative drowsiness or re sedation, which can prolong the stay in the PACU (Zhang et al. 2024). In some surgical types, for example, urological surgeries under general anesthesia, the temporary decrease in the quality of postoperative recovery associated with remimazolam may have clinical significance (Mao et al. 2022). In comparison with inhalational anesthetics, remimazolam exhibits either superior or non-inferior postoperative recovery quality, especially in reducing PONV and enhancing psychological support (Lee et al. 2024). It maintains a more stable hemodynamic state, with smaller fluctuations in blood pressure and heart rate during the operation, and requires lower doses of vasopressor drugs. In certain surgical types like laparoscopic cholecystectomy, remimazolam significantly reduces the incidence of PONV (Song et al. 2022). To sum up, remimazolam presents certain advantages in terms of postoperative recovery quality. It can ensure more stable hemodynamics during the peri-operative period, reduce PONV, and improve psychological support and emotional state. Consequently, it is expected to be a clinically feasible alternative to propofol for routine sedation.

In clinical anesthesia, combined anesthesia is widely used. The combination of intravenous anesthetics and inhalational anesthetics can not only strengthen the depth and stability of anesthesia and improve hemodynamics but also decrease the risks related to the dosage of a single drug. Taking into account multiple factors such as anesthesia efficacy and drug safety, it is essential to use remimazolam in combination with inhalational anesthetics for the maintenance of intraoperative anesthesia. Recently, Fu Shi et al. (2024) explored the application of remimazolam in combination with 0.6% sevoflurane in pituitary adenectomy. This was the first clinical study to investigate the combined use of remimazolam and inhaled anesthetics. Their findings demonstrated that this combination could maintain stable hemodynamics and an appropriate depth of anesthesia while causing few adverse reactions. Huang et al. (2024) then examined the minimum alveolar concentration of sevoflurane combined with remimazolam in adults during laryngeal mask airway insertion. They proved that this combination could be safely and effectively used for anesthesia induction, with remimazolam reducing the MAC value of sevoflurane during inhalation-induced anesthesia. Our research further corroborated these findings, showing that the use of remimazolam combined with 0.5 MAC sevoflurane is safe and effective for the maintenance of general anesthesia in elderly patients undergoing laparoscopy; and this combination provides a better overall postoperative QoR-15 score compared to remimazolam-based total intravenous anesthesia. We consider that the combined use of sevoflurane can improve the quality of postoperative recovery, mainly because sevoflurane can reduce postoperative inflammatory reactions. In animal experiments (Han et al. 2024), the levels of inflammatory cytokines in mice exposed to sevoflurane anesthesia are decreased. Some studies have shown that during general anesthesia, sevoflurane protects the lung function of elderly patients (Yao et al. 2023) by

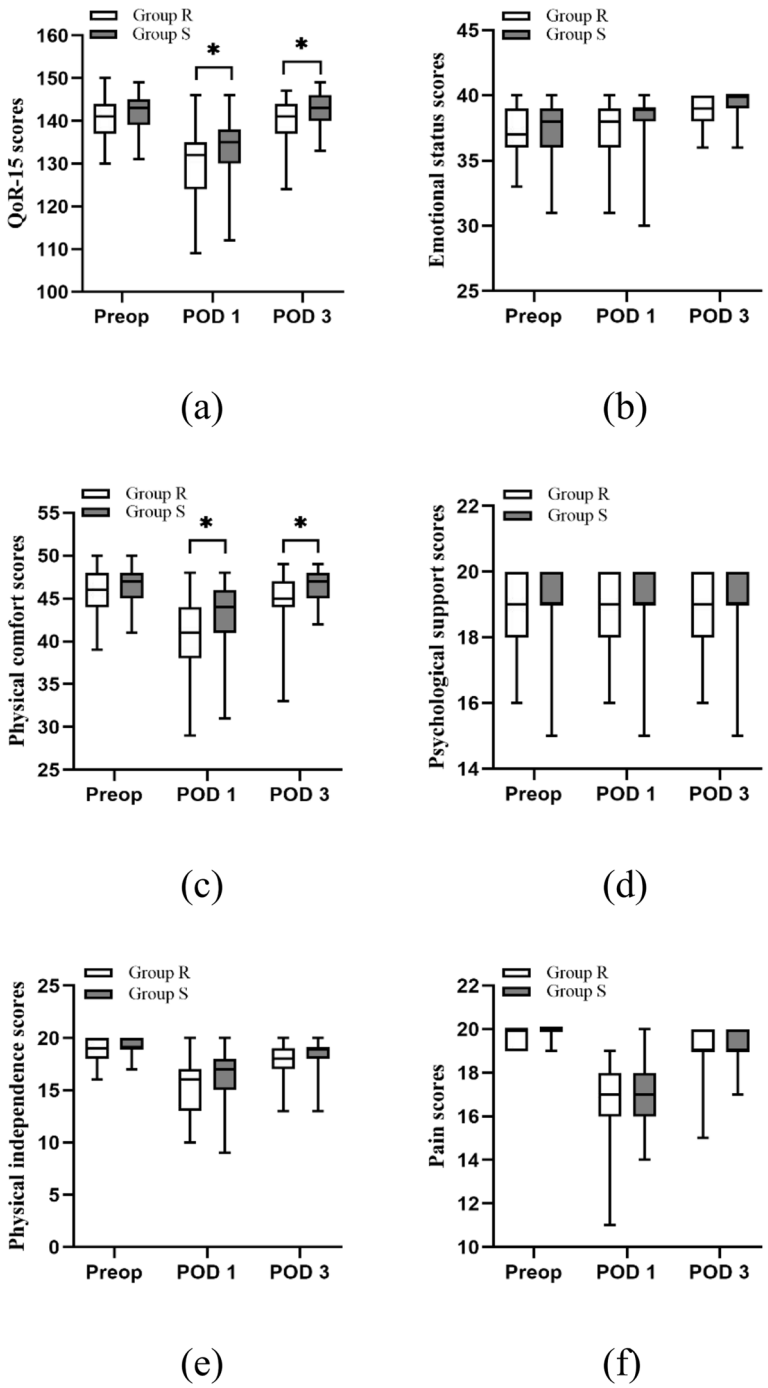

Fig. 2 Total QoR-15 score and sub-scores of the five dimensions of the QoR-15. Boxplots represent the median, as well as the 25% and 75% interquartile range. **a** Total QoR-15 score, **b** emotional state, **c** Physical comfort, **d** psychological support, **e** physical independence, **f** pain. *$P < 0.05$. POD, postoperative day; Preop, preoperative; QoR, quality of recovery

reducing inflammation and oxidative stress reactions and relieving postoperative pain. Sevoflurane can also prevent inflammatory reactions and myocardial injury after cardiopulmonary bypass surgery (Karacaer et al. 2023). When the inflammatory reaction is alleviated, the internal environment of the body is more stable, which is conducive to tissue repair and function recovery, and this directly promotes the improvement of postoperative recovery. The recovery of brain function is crucial to the overall recovery. The regulatory effect

Table 4 Comparison of induction time and awake time of anesthesia in two groups of patients

	Group R	Group S	*P*-value
Time to loss of consciousness (min)	2.3(0.5)	2.3(0.5)	0.752
Time to extubation (min)	24.0[21.0]	32.0[16.0]	0.048*

The values are expressed as means (SD) or median [inter-quartile range]

* $P < 0.05$

of sevoflurane on the central nervous system may help maintain the stable state of the brain during anesthesia and after surgery. Some studies on neurotransmitters indicate that sevoflurane produces sedative, hypnotic, and anti-anxiety effects by enhancing the GABA (Mapelli et al. 2021) system, which helps to reduce the stress response of patients during surgery and is beneficial to the recovery of physical functions after surgery.

Even if our preliminary research (Fei et al. 2023) implied that the use of remimazolam for the induction and maintenance of general anesthesia in elderly patients could sometimes lead to situations such as persistent intraoperative hypertension that requires antihypertensives, or BIS values above 60 necessary for corrective actions, there was no intraoperative hypertension observed in either group of patients in our study. This may be attributed to the inclusion of patients in the preliminary study: patients included were those who underwent thoracoscopic surgery, where the depth of anesthesia was hard to control, and intense surgical stimulus (such as tracheal traction and compression of the heart) could easily cause transient hypertension and a BIS value greater than 60 due to light anesthesia. However, the current study mainly included patients undergoing laparoscopic hernia repair or gallbladder surgery, which involved less intense surgical stimulus. The anesthesia given in both groups was deep enough for surgery so that the effectiveness of the combination of remimazolam and sevoflurane could be proved. Besides, there was no significant difference in the incidence of postoperative nausea and vomiting between the two groups, indicating that the additional use of sevoflurane did not increase the risk of nausea and vomiting in elderly patients after laparoscopic surgery. Bansal et al.'s prospective study (2022) found that combining propofol with sevoflurane resulted in a similar rate of postoperative nausea and vomiting following laparoscopic surgery as propofol alone. So, it can be

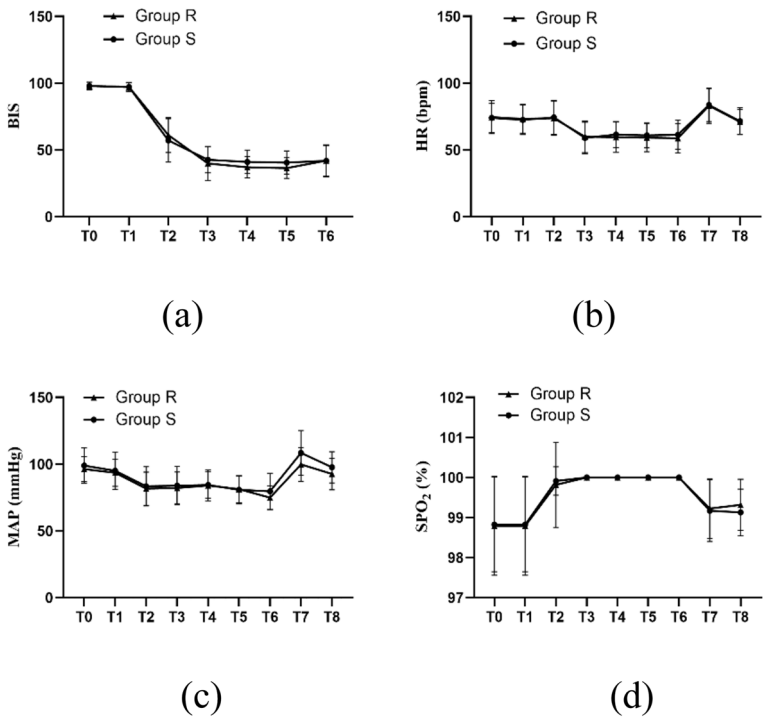

Fig. 3 Perioperative hemodynamic variables including **a** BIS, **b** HR, **c** MAP, **d** SpO_2. T0: arrive at the operating room; T1: before induction; T2: 1 min after induction; T3: the beginning of surgery; T4: 15 min after the surgery; T5: 30 min after the surgery; T6: the end of surgery; T7: after extubation; T8: discharge from PACU; BIS, bispectral index; HR, heart rate; MAP, mean arterial pressure; SpO_2, pulse oxygen saturation; PACU, post-anesthesia care unit

Table 5 Comparison of intraoperative doses of norepinephrine, remimazolam, and remifentanil between two groups

	Group R	Group S	*P*-value
Total amount of norepinephrine (mcg)	170.0[240.0]	240.0[180.0]	0.102
Total amount of remifentanil (mcg)	1234.0[609.0]	1000.0[450.0]	0.021*
Total amount of remimazolam (mg)	71[36.0]	68[16.0]	0.264

The values are expressed as median [inter-quartile range]

* $P < 0.05$

Table 6 Comparison of the incidence of perioperative adverse events between two groups

	Group R	Group S	*P*-value
Injection pain, *n*(%)	0(0.0)	0(0.0)	1.000
Hypotension, *n*(%)	1(2.0)	2(3.9)	1.000
Hypertension, *n*(%)	0(0.0)	0(0.0)	1.000
Bradycardia, *n*(%)	1(2.0)	0(0.0)	0.982
PONV, *n*(%)	1(2.0)	1(2.0)	1.000
Intraoperative awareness, *n*(%)	0(0.0)	0(0.0)	1.000
Delayed emergence, *n*(%)	2(3.9)	1(2.0)	0.969
Anaphylactic reaction, *n*(%)	1(2.0)	0(0.0)	0.982

The values are expressed as no. (%)

PONV postoperative nausea and vomiting

suggested to add sevoflurane in smaller doses to the infusion of remimazolam for the maintenance of anesthesia.

Our study revealed that the success rate of intravenous remimazolam (6 mg/kg/h) administration for inducing general anesthesia in elderly patients was almost 100%, with no serious adverse effects reported. This method notably decreased the risk of hypotension and injection pain in elderly patients undergoing general anesthesia, despite a slightly prolonged time for patients to lose consciousness and fall asleep. During the induction with remimazolam intravenous infusion, about 70% of patients showed a physiological yawning-like response similar to that during natural sleep. Research shows that yawning may be related to brain cooling and increased alertness and is a thermoregulatory mechanism (Gallup and Eldakar 2011; Gallup and Gallup 2008). However, the specific mechanism by which remimazolam injection induces yawning remains unclear and may be related to the slow-induction method that simulates the physiological way of sleep.

In this study, the average extubation time in the sevoflurane group was longer than that of the remimazolam group. This result contradicted our initial hypothesis that using a low concentration of sevoflurane during the operation would reduce the amount of remimazolam needed and that sevoflurane could be rapidly metabolized through lung tissue by adjusting oxygen flow at the end of the procedure to facilitate quicker emergence. One possible explanation for this situation is that the combination of drug interactions may cause sedatives to take longer to clear completely from the central nervous system (Zhang et al. 2024).

Delayed recovery (Kempenaers et al. 2023) after using remimazolam anesthesia has been documented in some studies. Remimazolam is primarily metabolized by the nonspecific esterase CES1 in the liver and lung, and the activity of this enzyme may be diminished due to acute liver failure. Besides, higher BMI, advanced age, and hypoproteinemia are considered risk factors for delayed recovery (Kempenaers et al. 2023). In our study, two patients in Group R and one in Group S failed to open their eyes when called 1 h after the cessation of the anesthetic injection, but their tidal volume and respiratory rate were normal, and vital signs were stable for endotracheal intubation. Later, we administered flumazenil, to reverse the effects of sedatives in these three patients. Sixty seconds after the administration of 0.2 mg flumazenil, all three patients were able to open their eyes when called, follow instructions, and reach a sufficient level of wakefulness for successful removal of the tracheal catheter, with no recurrence of sedation observed. The fact that flumazenil can reliably reverse the sedative effects of remimazolam suggests that remimazolam can be safely used for prolonged sedation and this sedation can be quickly reversed by flumazenil. Even so, re-sedation (Yamamoto et al. 2021; Masui 2023) after remimazolam administration has been observed in several studies. Some researchers argue that factors such as the lower total clearance of large doses of flumazenil and remimazolam may be contributing to this issue. In addition, given that flumazenil can be rapidly metabolized by the liver, the elimination of flumazenil may be faster than that of remimazolam, which may lead to the recurrence of sedation (Masui 2023). However, the precise mechanism behind re-sedation after flumazenil administration remains unclear.

Although remimazolam is generally promoted as a safe medication for general anesthesia, with minimal effects on hemodynamics and only mild respiratory depression, it has also been reported to cause anaphylactic shock. For instance, a 32-year-old male patient (Tsurumi et al. 2021) suddenly experienced facial flushing, hypotension, and lower SpO_2 just 2 min after the remimazolam infusion for anesthesia induction in his hand surgery. The patient's vital signs were stabilized through the repeated intravenous bolus of epinephrine. Four weeks post-surgery, the patient tested positive for allergies to both remimazolam

and midazolam in intradermal allergy testing. Given that remimazolam is structurally derived from midazolam, there is a potential risk of cross-resistance or allergy when remimazolam is used in combination with other benzodiazepines. The type I hypersensitivity reaction is a rare but serious adverse event with an unclear pathophysiology. In the above case, the patient may have experienced a mild immune reaction after exposure to midazolam four weeks earlier, but our busy anesthesiologists overlooked certain details. For example, a skin rash on the patient's body that was not discovered or given attention to due to being covered up. However, at this point, the patient's immune system may have already started producing corresponding antibodies. So, when the patient was then given general anesthesia with remimazolam, which shares structural similarities with midazolam, he experienced hypersensitivity reactions and anaphylactic shock because he was re-exposed to an allergen similar to the one that he had encountered previously. In our study, another patient developed a mild red rash on the palm and forearm of the arm with IV access approximately 2 min after receiving an intravenous infusion of remimazolam (6 mg/kg/h) for induction. However, the patient's vital signs remained stable. Since the patient did not fall asleep at the time, and reported no disform when asked, we gave him treatment for allergic reactions. The rash subsided after around 10 min. We can almost attribute this rash to the remimazolam infusion because no preoperative intravenous antibiotics were administered before the remimazolam injection, and our intravenous push of other anesthetics would not start until the patient's MOAA/S score dropped below 1 after the use of remimazolam for induction. As this patient had no medical history of food or drug allergies, surgical history, or prior use of benzodiazepines (such as sleeping pills or antiepileptics), if the rash caused by the intravenous infusion of remimazolam had not been detected promptly, or if the patient had not been informed post-surgery about the potential for a benzodiazepine allergy, the consequences could be fatal in the event of accidental benzodiazepine use in the future.

The clinical trial faced limitations, including being a single-center study with potential variability in experimenter experience and oversight and enrolling only elderly patients for short laparoscopic gallbladder and hernia surgeries. The impact of remimazolam-based anesthesia and remimazolam-sevoflurane combination on recovery quality for longer surgeries remains unclear. A multicenter, large-sample study is needed to further validate the effects of this combination on elderly patients' post-general anesthesia recovery.

Conclusions

In elderly patients undergoing minor laparoscopic abdominal surgery, the application of remimazolam combined with sevoflurane in the anesthesia leads to better postoperative recovery quality compared to using remimazolam alone. Besides, the combination of remimazolam and sevoflurane can reach an optimal depth of anesthesia, with no obvious adverse events or complications.

Abbreviations

Group R	Remimazolam group
Group S	Remimazolam-sevoflurane combination group
QoR	Quality of recovery
POD	Postoperative day
Preop	Preoperative
ERAS	Enhanced recovery after surgery
MOAA/S	Modified Observer's Assessment of Alertness and Sedation
CONSORT	Consolidated Standards of Reporting Trials
ASA	American Society of Anesthesiologists
ECG	Electrocardiograph
HR	Heart rate
SpO_2	Pulse blood oxygen saturation
BIS	Bispectral index
MAP	Mean arterial pressure
BMI	Body mass index
LoC	Loss of consciousness
MAC	Minimal alveolar concentration
PACU	Post-anesthesia care unit
SD	Standard deviation
IQR	Interquartile range
PONV	Postoperative nausea and vomiting

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None.

Authors' contributions

X. and Z.helped conception, design and administrative support. L., S. and C. helped data collection, analysis and manuscript writing. L. and G. helped data analysis and interpretation. L. helped collection and assembly of data. X. and L. helped manuscript revising. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This research is a randomized controlled clinical trial and was approved by the Ethics Committee of the Tenth Affiliated Hospital of Southern Medical University (KYKT2022-028-B2). It was registered at the Chinese Clinical Trial Registry (ChiCTR2200065332). Written informed consent will be obtained from the patients or legal guardians before participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, Shenzhen Traditional Chinese Medicine Hospital, The Fourth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine, Shenzhen 518033, China. [2]Department of Anesthesiology, Dongguan People's Hospital, The Tenth Affiliated Hospital of Southern Medical University, Dongguan 523000, China. [3]Southern Medical University, No. 1023, South Sha Tai Road, Jingxi Street, Baiyun District, Guangzhou 510000, China. [4]Guangdong Medical University, No. 2 East Wenming Road, Xiashan District, Zhanjiang 524000, China. [5]Department of Anesthesiology, Nanhai District People's Hospital of Foshan, The Sixth College of Clinical Medicine, South China University of Technology, Foshan 528000, China. [6]Dongguan Key Laboratory of Anesthesia and Organ Protection, Dongguan, China.

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