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The effects of remimazolam in combination with estazolam on postoperative hemodynamics and pain intensity in patients undergoing laparoscopic gastrointestinal surgery

Bai Sun[1] and Xianglong Sun[2*]

Abstract

Objective This study aimed to investigate the effects of combining remimazolam with estazolam on hemodynamics and pain levels after laparoscopic gastrointestinal surgery.

Methods A total of 184 patients who underwent laparoscopic gastrointestinal surgery were enrolled in this double-blind randomized controlled trial. The patients were divided into four groups: Study Group 1(Remimazolam), Study Group 2(Estazolam), Study Group 3(Remimazolam + Estazolam), and Control Group. Anesthesia induction included intravenous injection of remimazolam and estazolam in the study groups, while the control group received normal saline. Hemodynamic parameters, stress responses, anxiety levels, and pain intensity were assessed at various time points.

Results The results showed that the combination of remimazolam and estazolam significantly improved hemodynamic parameters compared to the control group. Study Group 3 exhibited the lowest anxiety levels and stress responses among all groups. Furthermore, Study Group 3 had the lowest pain intensity scores at different postoperative time points.

Conclusion The combination of remimazolam and estazolam effectively stabilized hemodynamics, reduced anxiety levels, and alleviated pain intensity after laparoscopic gastrointestinal surgery. These findings suggest that this combination therapy has the potential to improve surgical outcomes and patient comfort.

Keywords Laparoscopic gastrointestinal surgery, Hemodynamics, Remimazolam, Estazolam

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Background

The gastrointestinal tract is the most vital component of the body's digestive system. It is susceptible to various diseases, such as intestinal obstruction, rectal cancer, gastric cancer, appendicitis, and gastroenteritis, which can cause discomfort and abdominal pain in patients. Reduced appetite and disease progression can even lead to fatalities. Treatment options for gastrointestinal disorders include dietary therapy, surgical intervention, and medication [1]. However, compared to non-surgical treatments, surgical intervention may evoke concerns, fear, and anxiety in some patients due to a lack of relevant knowledge. These negative emotions can potentially affect the surgical process, increase intraoperative risks, and contribute to postoperative complications, thus impeding the effectiveness of surgical treatment [2, 3].

With the continuous development of laparoscopic techniques, laparoscopic gastrointestinal surgery has become a common clinical practice [4]. Its advantages, such as minimal invasiveness, reduced complications, and faster recovery, have led to widespread clinical application. However, hemodynamic parameters in perioperative patients typically exhibit an upward trend, which can adversely impact the surgical outcomes [5]. Gastrointestinal surgery can influence blood dynamics, particularly blood pressure and cardiac function. In a study by Ren [6] et al., it was found that combined anesthesia, including epidural anesthesia and general anesthesia, could reduce stress responses during major abdominal surgery but also lead to moderate hemodynamic instability. Therefore, maintaining stable perioperative hemodynamics is of paramount importance for ensuring smooth surgery and improving surgical outcomes.

Remimazolam is a newly introduced sedative that acts on the GABA (Gamma-Aminobutyric Acid) A receptor, enhancing the activity of GABA receptors containing the γ subunit [7]. Due to the higher concentration of extracellular chloride ions compared to intracellular levels, chloride ions enter the cells along the concentration gradient, leading to intracellular hyperpolarization and reduced excitability. This inhibits neuronal electrical activity and produces sedative effects. Compared to other sedatives, remimazolam anesthesia has been found to better maintain hemodynamic stability [8–10]. Estazolam is a medication with multiple medical applications. It has been shown to be effective in treating periodontitis in patients with diabetes. With regards to its hypnotic effects, estazolam has been found to significantly improve sleep parameters in adults with chronic insomnia, remaining effective even with nightly administration for at least six weeks [11]. Estazolam has also been found to be an effective sedative for preoperative use, providing long-lasting sedation without severe complications. Additionally, estazolam possesses properties such as anxiety control, antiepileptic effects, and muscle relaxant properties [12, 13]. Wang [14] et al. have indicated that the combination of remimazolam and estazolam can effectively alleviate patient anxiety, thereby stabilizing hemodynamic levels. Therefore, this study aims to investigate the effects of combining remimazolam with estazolam on hemodynamics and pain levels after laparoscopic gastrointestinal surgery.

Materials and methods

General information

A total of 184 patients who underwent laparoscopic gastrointestinal surgery at our hospital from February 2021 to May 2023 were enrolled in this study. The patients were randomly divided into four groups: Study Group 1, Study Group 2, Study Group 3, and Control Group, with 46 patients in each group. This study protocol complied with the relevant requirements of the Declaration of Helsinki by the World Medical Association.

Inclusion and exclusion criteria

Inclusion criteria: Patients undergoing laparoscopic gastrointestinal surgery; American Society of Anesthesiologists (ASA) [15] classification grade I-III; clear consciousness during the perioperative period; no history of central nervous system disorders or psychiatric illnesses; no sedative or hypnotic medication within the past year; no preoperative cognitive impairment; no contraindications to anesthesia. Exclusion criteria: Previous gastrointestinal functional disorders; severe impairment of cardiac, pulmonary, hepatic, or renal function; allergy to the study drugs; history of oral sedative or analgesic medication within the past 14 days; change in surgical approach during the operation; surgical duration exceeding 2 h; intraoperative hemorrhage exceeding 200 mL per hour or total intraoperative hemorrhage exceeding 800 mL; previous history of laparoscopic surgery.

Methods

Anesthesia Technique: All patients fasted for 2 h and abstained from drinking for 8 h before surgery. Routine monitoring of SpO2 (Peripheral Capillary Oxygen Saturation), DBP (Diastolic Blood Pressure), SBP (Systolic Blood Pressure), and ECG (Electrocardiogram) was performed, and a peripheral venous access was established. The night before surgery, patients in Study Group 2 and Study Group 3 took 1 mg of estazolam orally before sleep. Fifteen minutes before anesthesia induction, patients in Study Group 1 and Study Group 3 received intravenous injection of 0.1 mg/kg remimazolam (prepared with normal saline at a concentration of 1 mg/mL), while patients in Study Group 2 and the Control Group received intravenous injection of 0.1 mL/kg normal saline. Anesthesia induction included sequential intravenous administration

of 0.3 μg/kg sufentanil, 2 mg/kg propofol, and 0.15 mg/kg cisatracurium. After 3 min, endotracheal intubation was performed, and the respiratory parameters were set as follows: tidal volume (VT) of 6–8 mL/kg, I:E ratio of 1:2, FiO2 of 60%, and respiratory rate (RR) adjusted to 8–12 breaths per minute according to intraoperative conditions, maintaining PETCO2 at 35–45 mmHg. Anesthesia maintenance included continuous intravenous infusion of 5 mg/kg/h propofol and 0.10 μg/kg/min remifentanil. Cisatracurium was administered as a bolus of 0.03 mg/kg as needed to maintain muscle relaxation, and vasopressor drugs were used to maintain heart rate (HR) and blood pressure (BP) fluctuations within 20% of baseline values when necessary. Propofol and remifentanil were discontinued during skin closure. When extubation criteria were met, the endotracheal tube was removed, and the patient was transferred to the post-anesthesia care unit. Ramsay Sedation Scale was assessed 30 min later, and once the discharge criteria were met, the patient was sent back to the ward.

Observation indicators

Comparisons were made between different time points [before induction of anesthesia (T0), before tracheal intubation (T1), immediately after intubation (T2), 10 min after pneumoperitoneum (T3), and immediately after extubation (T4)] for hemodynamic parameters, as well as at different postoperative time points [30 min, 6 h, 12 h, 24 h, 48 h] for pain intensity. Surgery-related details and occurrence of complications were recorded, and preoperative and postoperative stress responses and anxiety levels were observed.

Surgery-related details included the duration of surgery, extubation time, time to respiratory recovery, and time to awakening.

Hemodynamics: Changes in hemodynamic parameters (HR, SpO2, MAP) were compared between T0, T1, T2, T3, and T4.

Stress Response: Five milliliters of venous blood samples were collected from patients before and after surgery, centrifuged, and sent for analysis using radioimmunoassay to measure norepinephrine (NE), epinephrine (E), and cortisol (Cor) levels.

Anxiety Levels: State-Trait Anxiety Inventory (STAI) [16]was used to assess anxiety levels during the preoperative visit, upon entering the operating room, and 10 min after saline infusion. The total score ranges from 20 to 80, with higher scores indicating higher levels of anxiety.

Pain Intensity: Pain was evaluated using the Visual Analog Scale (VAS) [17] at 30 min, 6 h, 12 h, 24 h, and 48 h postoperatively. Scores range from 0 to 10, with higher scores indicating higher levels of pain intensity.

Occurrence of Postoperative Complications: This includes nausea, abdominal distension, agitation during the emergence period, and vomiting.

Statistical analysis

Data processing was performed using SPSS 21.0 statistical software. For normally distributed continuous variables, mean ± standard deviation (mean ± sd) was used to represent the data. Between-group comparisons were analyzed using independent samples t-test or one-way analysis of variance (ANOVA). For variables that did not follow a normal distribution, median (interquartile range) [M(P25, P75)] was used to represent the data. Between-group comparisons were analyzed using the Mann-Whitney test or Kruskal-Wallis test. Categorical data was presented as frequencies (percentages) [n(%)] and between-group comparisons were analyzed using the chi-square test or Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

Results

Comparison of general information

We compared gender, age, smoking habits, alcohol consumption, BMI (Body Mass Index) values, and ASA among the different groups and found no statistically significant differences. Among them, Study Group 1 consisted of 21 males and 25 females, aged 31 to 65 years with a mean age of (49.08 ± 9.07) years; Study Group 2 consisted of 20 males and 26 females, aged 30 to 66 years with a mean age of (49.19 ± 11.08) years; Study Group 3 consisted of 22 males and 24 females, aged 30 to 65 years with a mean age of (49.27 ± 10.82) years; and the Control Group consisted of 21 males and 25 females, aged 30 to 63 years with a mean age of (49.32 ± 10.07) years. As shown in Table 1.

Comparison of surgical characteristics among the groups

The surgical duration, extubation time, time to respiratory recovery, time to awakening, anesthesia duration, propofol dosage, and remifentanil dosage were compared among the groups. The results revealed no statistically significant differences among the groups ($P > 0.05$), as presented in Table 2.

Comparison of hemodynamic parameters among the groups

At time points T0 and T4, there were no statistically significant differences in HR, SpO2, and MAP levels among the groups ($P > 0.05$). However, at time points T2 and T3, there were significant differences ($P < 0.05$) in HR, SpO2, and MAP between Study Groups 1, 2, and 3 compared to the Control Group. There were no statistically significant differences in HR, SpO2, and MAP among Study Group

Table 1 Comparison of general information of the groups

Item	Study group 1($n=46$)	Study group 2($n=46$)	Study group 3($n=46$)	Control group($n=46$)	t/χ^2	*p*
Sex (male)	21	20	22	21	0.175	0.982
Age (years)	49.08 ± 9.07	49.19 ± 11.08	49.27 ± 10.82	49.32 ± 10.07	0.053	0.958
Smoking	5	4	5	6	0.449	0.930
Alcohol consumption	4	5	4	6	0.646	0.886
BMI (kg/m2)	22.98 ± 3.09	23.08 ± 3.17	23.26 ± 3.03	22.87 ± 3.11	1.379	0.171
ASA					0.772	0.856
Grade I	20	22	18	21		
Grade II	26	24	28	25		
Primary Disease					0.763	0.858
Laparoscopic repair of gastrointestinal perforation	20	22	21	24		
Gastrointestinal mesenchymal tumor	26	24	25	22		

Table 2 Comparison of basic surgical conditions between groups

Item	Study group 1($n=46$)	Study group 2($n=46$)	Study group 3($n=46$)	Control group($n=46$)	t	*p*
Surgical time (min)	118.65 ± 20.81	116.73 ± 19.76	122.87 ± 20.03	118.99 ± 20.38	0.454	0.651
Extubation time(h)	13.28 ± 3.19	13.76 ± 2.38	13.16 ± 2.43	12.97 ± 3.18	0818	0.416
Respiratory recovery time(h)	5.17 ± 1.38	5.09 ± 1.29	5.26 ± 1.32	5.07 ± 1.45	0.287	0.775
Awake time(h)	6.56 ± 1.45	6.61 ± 1.38	6.98 ± 1.27	6.23 ± 1.43	0.169	0.866
Propofol dosage (mg)	329.76 ± 20.33	327.98 ± 22.76	321.76 ± 25.09	333.98 ± 23.91	0.912	0.364
Remifentanil dosage (mg)	530.76 ± 24.87	532.67 ± 25.81	529.87 ± 23.18	535.98 ± 22.87	1.048	0.298
Anesthesia time(h)	123.98 ± 19.98	122.76 ± 18.76	124.93 ± 19.97	125.71 ± 20.93	0.059	0.953

Table 3 Hemodynamic comparison between groups

Item	Time	Study group 1($n=46$)	Study group 2 ($n=46$)	Study group 3 ($n=46$)	Control group($n=46$)	t	*p*
HR(time/min)	T0	78.32 ± 8.48	78.68 ± 8.76	78.89 ± 8.09	78.41 ± 8.21	0.052	0.959
	T1	65.83 ± 7.89	65.34 ± 7.92	67.97 ± 7.83	63.87 ± 8.47	1.148	0.254
	T2	71.98 ± 8.36	72.97 ± 10.92	76.98 ± 10.73	64.43 ± 9.03	4.161	0.001
	T3	79.27 ± 9.19	80.09 ± 9.03	73.28 ± 8.76	86.02 ± 7.98	3.761	0.001
	T4	77.97 ± 9.03	76.83 ± 8.96	75.87 ± 8.97	78.67 ± 8.36	0.386	0.701
SpO_2(%)	T0	98.87 ± 9.76	98.34 ± 8.93	99.03 ± 9.08	98.38 ± 9.36	0.246	0.806
	T1	94.37 ± 8.93	94.97 ± 8.09	96.89 ± 8.18	90.01 ± 8.76	2.364	0.020
	T2	92.98 ± 8.78	92.04 ± 9.18	96.32 ± 9.87	88.87 ± 8.93	2.226	0.029
	T3	93.86 ± 9.93	93.19 ± 9.87	96.09 ± 9.92	89.28 ± 9.54	2.256	0.027
	T4	95.98 ± 9.65	96.56 ± 9.79	98.14 ± 9.09	95.02 ± 9.89	0.472	0.638
MAP(mmHg)	T0	88.76 ± 7.94	87.47 ± 9.43	88.93 ± 8.39	87.03 ± 7.38	1.006	0.317
	T1	80.98 ± 8.76	79.57 ± 8.45	84.98 ± 8.92	76.93 ± 8.47	2.254	0.027
	T2	92.98 ± 9.65	91.98 ± 8.93	87.94 ± 9.87	99.76 ± 9.06	3.474	0.001
	T3	84.97 ± 9.76	83.76 ± 9.91	88.92 ± 9.35	96.87 ± 8.93	6.101	<0.001
	T4	91.95 ± 8.76	90.67 ± 8.35	89.48 ± 8.49	93.97 ± 8.65	1.113	0.269

Note: Heart Rate (HR), mean Arterial Pressure (MAP), arterial Oxygen Saturation (SpO_2); before induction of anesthesia (T0), before tracheal intubation (T1), immediately after intubation (T2), 10 min after pneumoperitoneum (T3), and immediately after extubation (T4)

1, Study Group 2, and Study Group 3 ($P>0.05$), as shown in Table 3.

Comparison of anxiety levels among the groups

At the preoperative 1-day visit and upon admission, there were no statistically significant differences in anxiety levels among the groups ($P>0.05$). However, after 10 min of receiving normal saline, Study Group 1, Study Group 2, and Study Group 3 exhibited lower anxiety levels compared to the Control Group, and Study Group 3 showed lower anxiety levels compared to Study Group 1 and Study Group 2, with statistically significant differences ($P<0.05$). There were no statistically significant differences in anxiety levels among Study Group 1, Study Group 2, and Study Group 3 ($P>0.05$), as shown in Table 4.

Table 4 Comparison of anxiety level among groups (score)

Time	Study group 1 (*n* = 46)	Study group 2 (*n* = 46)	Study group 3 (*n* = 46)	Control group (*n* = 46)	t	*p*
At 1d preoperative visit	3.98 ± 1.28	3.91 ± 1.32	3.86 ± 1.37	3.82 ± 1.23	0.611	0.543
After admission to the room	3.37 ± 1.22	3.29 ± 1.03	3.32 ± 1.02	3.93 ± 1.34	2.96	0.039
After 10 min of saline	1.71 ± 0.37	1.81 ± 0.39	1.56 ± 0.35	4.13 ± 1.28	12.319	<0.001

Scoring according to the State-Trait Anxiety Inventory

Table 5 Comparison of stress response among groups

Item	Time	Study group 1 (*n* = 46)	Study group 2 (*n* = 46)	Study group 3 (*n* = 46)	Control group (*n* = 46)	t	*p*
NE(pmol/L)	Preoperative	2476.27 ± 31.28	2481.34 ± 30.91	2478.38 ± 29.91	2473.29 ± 29.67	0.469	0.640
	Postoperative	2876.91 ± 98.37	2880.09 ± 93.82	2598.29 ± 94.39	3309.37 ± 90.98	21.890	<0.001
E(pmol/L)	Preoperative	422.93 ± 22.65	421.83 ± 23.09	423.76 ± 23.28	424.97 ± 23.09	0.428	0.670
	Postoperative	481.94 ± 24.09	489.84 ± 23.38	463.87 ± 23.61	521.83 ± 24.38	7.894	<0.001
Cor(nmol/L)	Preoperative	436.87 ± 23.83	437.92 ± 22.38	435.95 ± 21.29	439.98 ± 20.38	0.673	0.503
	Postoperative	479.91 ± 22.91	477.93 ± 23.36	452.19 ± 22.87	543.29 ± 24.39	12.846	<0.001

Note: Norepinephrine (NE), epinephrine (E), and cortisol (Cor)

Table 6 Comparison of pain levels in each group (score)

Time	Study group 1 (*n* = 46)	Study group 2 (*n* = 46)	Study group 3 (*n* = 46)	Control group (*n* = 46)	t	*p*
30 min after surgery	3.81 ± 0.32	3.76 ± 0.39	3.89 ± 0.37	3.84 ± 0.43	0.380	0.706
6 h after surgery	2.81 ± 0.29	2.87 ± 0.34	2.79 ± 0.34	3.47 ± 0.39	9.210	<0.001
12 h after surgery	2.75 ± 0.32	2.79 ± 0.35	2.71 ± 0.32	3.29 ± 0.33	7.968	<0.001
24 h after surgery	2.45 ± 0.39	2.49 ± 0.41	2.41 ± 0.35	3.04 ± 0.45	6.720	<0.001
48 h after surgery	2.19 ± 0.38	2.23 ± 0.35	2.13 ± 0.39	2.91 ± 0.43	8.510	<0.001

Score measured using the Visual Analog Scale

Table 7 Comparison of adverse reactions among groups

Time	Study group 1 (*n* = 46)	Study group 2 (*n* = 46)	Study group 3 (*n* = 46)	Control group (*n* = 46)	t	*p*
Nausea	1	1	2	1		
Bloating	2	1	2	1		
Agitation during awakening	0	0	0	1		
Vomiting	0	0	0	0		
Total complication rate (%)	3(6.52)	2(4.35)	4(8.70)	3(6.52)	0.713	0.870

Comparison of stress responses among the groups

Prior to surgery, there were no statistically significant differences in NE, E, and Cor levels among the groups ($P>0.05$). However, postoperatively, Study Group 1, Study Group 2, and Study Group 3 exhibited lower levels of NE, E, and Cor compared to the Control Group. Additionally, Study Group 3 showed lower levels of NE, E, and Cor compared to Study Group 1 and Study Group 2, with statistically significant differences ($P<0.05$). Refer to Table 5 for details.

Comparison of pain levels among the groups

At 30 min postoperatively, there were no statistically significant differences in pain levels among the groups ($P>0.05$). However, at 6 h, 12 h, 24 h, and 48 h postoperatively, Study Group 1, Study Group 2, and Study Group 3 exhibited lower pain levels compared to the Control Group. Furthermore, Study Group 3 showed lower pain levels compared to Study Group 1 and Study Group 2, with statistically significant differences ($P<0.05$). As shown in Table 6.

Comparison of adverse reactions among the groups

We collected data on adverse reactions among the groups and found no significant differences among them ($P>0.05$), as shown in Table 7.

Discussion

In recent years, laparoscopic techniques have been continuously developed, particularly in laparoscopic gastrointestinal surgery. Compared to conventional open surgery, laparoscopic surgery offers advantages such as improved surgical visualization, reduced tissue damage, lower risk of infection, decreased intraoperative blood loss, faster postoperative recovery, fewer complications, shorter hospital stays, and lower medical costs. Although laparoscopic gastrointestinal surgery falls within the realm of gastrointestinal surgery, the insufflation of carbon dioxide for pneumoperitoneum can increase

intra-abdominal pressure, leading to the absorption of carbon dioxide into the bloodstream and the formation of hypercapnia. This can stimulate the sympathetic nervous system, thereby affecting the hemodynamics of the body [18, 19].

Effective anesthesia is a prerequisite for successful surgery and plays a crucial role in the smooth conduct of laparoscopic gastrointestinal surgery. The most commonly used anesthesia drugs in clinical practice currently include propofol and sufentanil, each with its own advantages and disadvantages. The active search for medications with enhanced analgesic and sedative effects is a current focus in the medical field. Remimazolam is a newly developed ultra-short-acting benzodiazepine-class drug. It reaches peak blood concentration within 1 min and has a terminal half-life of 0.6–0.9 h. Remimazolam is rapidly metabolized by non-specific esterases in the body to form the inactive metabolite, zolazepam acid, allowing patients to recover quickly [20]. Remimazolam has been studied in various surgical procedures, including gastrointestinal surgeries. Multiple studies have compared the effects of remimazolam and propofol in different surgical settings. One study compared the impact of remimazolam and propofol on the recovery status of patients undergoing laparoscopic cholecystectomy. They found that remimazolam had a longer recovery time compared to propofol, but fewer hemodynamic changes were observed when using remimazolam [21]. Another study compared the combination of methohexital remimazolam and propofol to propofol alone in patients undergoing endoscopic procedures under sedation. The combination group had fewer adverse events, better sedation effects, and higher satisfaction among endoscopists compared to propofol alone [22]. Additionally, a study compared remimazolam and propofol in ambulatory general anesthesia. They found that remimazolam had a longer recovery time compared to propofol but exhibited higher safety in terms of hypotension and injection pain. Although specific information on remimazolam in gastrointestinal surgery is limited, these studies suggest that remimazolam may be a viable choice for sedation and anesthesia in various surgical procedures. Relevant studies indicate that remimazolam demonstrates favorable sedation effects and more stable hemodynamics in gastroscopy, colonoscopy, and bronchoscopy procedures [23, 24]. Considering that benzodiazepine-class drugs may prolong the recovery time after anesthesia and impact the quality of recovery.

Estazolam is a sedative-hypnotic drug that has been studied in cases of fatal poisoning and preoperative patients. In the study on fatal poisoning, a metabolomic approach based on liquid chromatography-high-resolution tandem mass spectrometry (LC-HR MS/MS) was used to analyze mouse plasma and brainstem samples. Discriminative classification models were created using metabolites such as phenylacetylglycine, creatine, and indole-3-lactic acid in plasma, and palmitic acid, creatine, and indole-3-lactic acid in the brainstem [25, 26]. In the study involving preoperative patients, estazolam was compared to zolpidem. The results showed that compared to zolpidem, estazolam improved sleep patterns, mood upon awakening, and had a lower incidence of side effects [27]. However, there is no specific information available regarding the use of estazolam in gastrointestinal surgery. The study results showed no significant differences in surgical time, extubation time, suction recovery time, awakening time, propofol dosage, remifentanil dosage, and anesthesia time among the groups ($P>0.05$), suggesting that the application of remimazolam in combination with estazolam in patients undergoing laparoscopic gastrointestinal surgery does not affect postoperative recovery. Gurunathan et al. [28] conducted a study indicating that the addition of benzodiazepine-class drugs as adjuvant therapy during colonoscopy did not prolong patient recovery time or affect overall recovery quality, which is consistent with the results of this study.

Surgical trauma can lead to intraoperative hemodynamic fluctuations, and the greater the increase in intraoperative hemodynamics, the higher the level of physiological arousal, which is closely related to surgical risk. Maintaining stable intraoperative hemodynamics through effective anesthesia is essential for ensuring surgical safety [29]. The results of this study showed that in the T1, T2, and T3 research groups of Study 1, Study 2, and Study 3, respectively, HR, SpO2, and MAP were superior to the control group, suggesting that the application of remimazolam in combination with estazolam in patients undergoing laparoscopic gastrointestinal surgery does not affect HR, SpO2, and MAP levels, thus ensuring hemodynamic stability. This may be attributed to the effective anti-anxiety effect of preoperative treatment with remimazolam combined with estazolam, as preoperative anxiety is a common clinical symptom, occurring in 20-80% of patients. Preoperative anxiety can activate the sympathetic system, leading to various negative effects and increased hemodynamic fluctuations during the perioperative period.

Surgical trauma and postoperative pain activate stress factors and increase prostaglandin secretion. Stimulation of the sympathetic nervous system during stress promotes the release of stress factors such as NE, E, and Cor [30]. Relevant literature indicates that administering analgesics to patients can alleviate the body's stress response. The results of this study showed that in the postoperative period, the levels of NE, E, and Cor in Study 1, Study 2, and Study 3 were lower than those in the control group. Additionally, in Study 3, the levels

of NE, E, and Cor were lower than those in Study 1 and Study 2 ($P<0.05$). This suggests that the application of remimazolam in combination with estazolam in patients undergoing laparoscopic gastrointestinal surgery does not increase the levels of NE, E, and Cor, and does not affect the stress response.

In summary, the application of remimazolam in combination with estazolam in patients undergoing laparoscopic gastrointestinal surgery does not affect HR, SpO2, and MAP levels, ensuring hemodynamic stability. It can alleviate anxiety, reduce the levels of NE, E, and Cor, decrease stress responses, and alleviate pain. Moreover, it has minimal adverse effects and promotes patient recovery, making it suitable for clinical application and further promotion.

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Author contributions
Bai Sun was responsible for data collection, statistical analysis, and interpretation, and wrote the manuscript. Xianglong Suninterpreted and supervised the statistical analysis and edited the manuscript. All authors approved the final version of the manuscript.

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Data availability
The datasets used and analyzed during the current study are available fromthe corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from Institutional Review board of Zhucheng People's Hospital. Written informed consent was taken from each participant and all participants' privacy and information was kept confidential. Additionally, the all methods were carried out in accordance with relevant institutional guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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