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Effect of remimazolam combined with estazolam on anxiety levels and postoperative gastrointestinal function recovery in patients undergoing laparoscopic cholecystectomy surgery

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Abstract

Purpose The objective of this study is to examine the impact of administering remimazolam and estazolam in alleviating preoperative anxiety on the recovery of gastrointestinal function in patients undergoing laparoscopic cholecystectomy surgery.

Materials and methods A total of 140 patients who were scheduled for elective laparoscopic cholecystectomy surgery were randomly divided into four groups using random number table: remimazolam group (group R, $n=35$), estazolam group (group E, $n=35$), remimazolam combined with estazolam group (group RE, $n=35$), and control group (group C, $n=35$). Group R received an intravenous injection of remimazolam before the administration of anesthesia, group E was orally administered estazolam on the night before surgery and intravenously injected with normal saline before induction of anesthesia, group RE received both estazolam orally on the night before surgery and intravenous injection of remimazolam before induction of anesthesia, and group C was given normal saline before induction of anesthesia. The visual analogue scale for anxiety (VAS-A) scores were documented during the preoperative visit, following entry into the operating room, and 10 min after intravenous remimazolam or normal saline. Time to the first postoperative exhaust and defecation, occurrence of nausea and vomiting within 24 h after surgery, sleep quality scores on the night before surgery and two nights after surgery as per Numerical Rating Scale (NRS), postoperative patient satisfaction, and occurrence of adverse reactions were also recorded.

Results In contrast to group C, time to the first postoperative exhaust and defecation of groups R, E, and RE were significantly reduced ($P<0.05$); the VAS-A scores of groups E and RE exhibited a significant decrease upon entering the operating room, and the VAS-A scores of groups R, E, and RE decreased significantly 10 min after intravenous remimazolam or normal saline ($P<0.05$); sleep quality scores of groups R, E, and RE were significantly higher on the first night after surgery ($P<0.05$). There was no significant difference in the occurrence of nausea and vomiting

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among the four groups within 24 h after surgery. No adverse reactions such as wound bleeding, infection, and severe abdominal distension occurred in the four groups.

Conclusions The utilization of remimazolam and estazolam, either singularly or in combination, before laparoscopic cholecystectomy surgery, has shown considerable efficacy in alleviating preoperative anxiety, and thus expediting the recovery of postoperative gastrointestinal function in patients. Moreover, the combination of both agents can improve the patient's postoperative sleep quality, thereby elevating patient satisfaction.

Keywords Preoperative anxiety, Postoperative gastrointestinal function, Remimazolam, Estazolam

Introduction

Accelerating the recovery of postoperative gastrointestinal function is not only one of the most important issues that the surgical field is facing today but also an important part of enhanced recovery after surgery (ERAS). Molina-Torres et al. pointed out in their research that anxiety and depression can affect the physiology of the gastrointestinal tract and cause gastrointestinal dysfunction through the brain–gut axis [1]. Preoperative anxiety is a prevalent emotion among patients who are about to undergo surgery and can adversely affect postoperative recovery [2]. Benzodiazepines (BZDs), first introduced in clinical practice in the 1960s, have become one of the most widely used sedative-hypnotic agents [3]. Due to their rapid onset and reliable efficacy, BZDs are commonly employed for the short-term treatment of symptoms, such as anxiety, insomnia, and agitation. They exert their pharmacological effects primarily by enhancing the inhibitory action of gamma-aminobutyric acid type A ($GABA_A$) receptors, which are located in various regions of the central nervous system, particularly the limbic system, including the amygdala, hippocampus, and prefrontal cortex. By modulating the α_2/α_3 subunits of these receptors, BZDs effectively regulate mood, anxiety, and seizure responses [4].

Remimazolam and Estazolam, both benzodiazepine derivatives, have shown notable advantages in anxiety treatment. Remimazolam, a novel ultra-short-acting BZD, is an ester-based compound that is rapidly hydrolyzed by tissue esterases into an inactive metabolite, resulting in rapid onset and short duration of action. Remimazolam selectively acts on $GABA_A$ receptors, demonstrating superior efficacy in sedation, hypnosis, and anxiolysis, with predictable effects and a short recovery time [5]. Compared to traditional BZDs, Remimazolam offers the advantages of reduced side effects and minimal drug accumulation in anesthetic induction and procedural sedation [6]. Studies have reported that intravenous administration of Remimazolam results in an onset time of 1–3 min and a recovery time of 5.5–20 min following discontinuation [7].

Estazolam is a triazolobenzodiazepine commonly used for treating insomnia. In addition to improving sleep, Estazolam is widely employed in managing anxiety symptoms, particularly in the treatment of generalized anxiety disorder [3]. Estazolam exerts its anxiolytic effects by binding to $GABA_A$ receptors, promoting chloride ion influx, and suppressing neuronal excitability. It is primarily metabolized in the liver, with a half-life of approximately 12–15 h [8]. Estazolam has proven effective in improving sleep quality and reducing nocturnal awakenings.

Therefore, this study aims to investigate the effects of applying two anxiolytics, remimazolam and estazolam, on the recovery of postoperative gastrointestinal function in patients undergoing laparoscopic surgery through alleviating preoperative anxiety and provide clinical evidence accordingly.

Materials and methods

Recruitment and randomization

This prospective randomized controlled double-blind study was approved by the Ethics Committee of the First People's Hospital of Lianyungang (registration number: KY-20211030001-01).The study conformed to the standards of the Declaration of Helsinki and registered at https://www.chictr.org.cn (ChiCTR2200057898).All participants were informed about the study, and written informed consent was obtained from them. Eligible participants were recruited in a tertiary center between January 2022 and May 2022. Inclusion criteria included patients expected for elective laparoscopic cholecystectomy surgery aged 18–64 years, regardless of gender, with BMI 18–28 kg/m^2 and visual analog scale for anxiety (VAS-A) > 0 (with a range of 0–10, a higher score indicates more severe anxiety), and classified as American Society of Anesthesiologists (ASA) physical status I or II. Exclusion criteria included a history of oral sedative-analgesic medication (benzodiazepines, barbiturates, NSAIDs, opioid analgesics, etc.) within 14d preoperatively; contraindications to the use of or allergic to benzodiazepines; severe cardiac, lung, liver, or kidney dysfunction; previous gastrointestinal dysfunction; inability to understand the meaning of the rating scale and history of mental illness. Elimination criteria included changing surgical procedures during surgery,

intraoperative haemorrhage > 800 mL or > 200 mL per hour, surgical time > 2 h, and loss of data at postoperative follow-up. Patients were allocated by random number table into four groups: remimazolam group (group R), estazolam group (group E), remimazolam combined with estazolam group (group RE), and control group (group C).

Anaesthesia methods

All patients were required to fast for 8 h and abstain from drinking for 2 h before surgery. After the patients were admitted to the operating room, standard intraoperative monitoring of electrocardiogram (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse oximetry (SpO_2) was conducted and intravenous (IV) access was established. All four groups were administered their respective medication by a nurse the night before the procedure: Group E and Group RE received 1 mg of Estazolam orally, while Group C and Group R received an equivalent oral placebo. 15 min before induction of anaesthesia, Remimazolam 0.1 mg/kg (1 mg/mL with normal saline) was given to group R and group RE, while normal saline 0.1 mL/kg was given to patients in group C and group E. Anaesthesia was induced with sufentanil 0.3 μg/kg, propofol 2 mg/kg, and cisatracurium 0.15 mg/kg. Tracheal intubation was performed 3 min after preoxygenation. The respiratory parameters were set to: V_T 6 ~ 8 mL/kg, I:E = 1:2, FiO_2 60%, RR 8–12 times/min (adjust as required), and $P_{ET}CO_2$ at 35–45 mmHg. Remifentanil (0.05–0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and propofol (4–6 $mg \cdot kg^{-1} \cdot h^{-1}$) were used for maintenance of general anesthesia by a syringe pump to maintain bispectral index (BIS) at 40–60. To maintain muscle relaxation, cisatracurium 0.03 mg/kg was administered as needed intravenously. When blood pressure and heart rate fluctuate out of a range of 20% of the basal level, vasoactive drugs were used for adjustment. Propofol and remifentanil were discontinued while suturing the skin. The endotracheal tube was removed when the indications for extubation were met, and then the patients were admitted to the post-anaesthesia care unit. Ramsay sedation score was measured 30 min after extubation, and patients were transferred to the ward when the relevant standard was met.

Outcomes

The state–trait anxiety inventory (STAI, with a range of 20–80, a higher score indicates more severe anxiety) at the preoperative visit was recorded, as well as the VAS-A scores at the preoperative visit, after admission to the operating room, and after 10 min of injecting either remimazolam or normal saline (anxiety was considered to be present if the VAS-A score was > 0) [9]. The time of anaesthesia, duration of surgery, intraoperative anaesthetic drug dosage, time of awakening, time to first postoperative exhaust, time to first defecation, duration of postoperative hospital stay, and occurrence of postoperative adverse reactions were recorded. Postoperative gastrointestinal function was assessed using the I-FEED score (containing intake, response to nausea treatment, emesis, exam, and duration, 0–2 points, normal; 3–5 points, postoperative gastrointestinal intolerance; ≥ 6 points, postoperative gastrointestinal dysfunction). Sleep quality scores (0, unable to sleep, very poor quality of sleep; 10, deep and satisfactory sleep) for the first preoperative night, the first and second postoperative nights were recorded, so as the occurrence of nausea and vomiting at 24 h postoperatively, the Ramsay sedation score (1 for anxious and agitated; 2 for tranquil; 3 for asleep but responding to commands; 4 for asleep but can be awakened; 5 for asleep and responding to stimuli; 6 for asleep and cannot be awakened) at 0.5 h postoperatively, and patient satisfaction scores (0 for "very dissatisfied", 10 for "very satisfied").

Sample size calculation

The time to first postoperative flatus was the primary outcome of this study. Based on our previous pilot study, we conducted a power analysis to calculate the sample size (G*power3.1 software). The means and standard deviations of the time to first flatus in the four groups (Group C, Group R, Group E, and Group RE) were 22 ± 6, 18 ± 6, 17 ± 5, and 20 ± 5, respectively, with 8 patients in each group. A common standard deviation of 6 and an effect size of 0.32 were calculated for each group. Based on an alpha error of 0.05 and a statistical power of 0.8, prior ANOVA analyses (F test) estimated that a total of 112 patients would be required, with at least 28 patients in each group. Considering a 20% dropout rate, a final sample size of 140 patients was needed.

Statistical analysis

We performed statistical analysis using the SPSS 25.0. Data were provided in the form of mean values ± standard deviation ($\bar{x} \pm s$) if the variables were normally distributed, and a one-way ANOVA was used for the intergroup comparisons. Conversely, a nonparametric test was used for the intergroup comparisons of non-normally distributed variables, which appeared as medians (M) and interquartile range (IQR). Categorical variables were expressed as number (%), and intergroup comparisons were made using the χ^2 test. Comparisons of ranked data were made using the rank-sum test. $P < 0.05$ was considered to be statistically significant.

Results

A total of 156 patients were assessed for eligibility, and 12 patients were excluded (Fig. 1). Of the 12 excluded patients, 4 patients refused consent, 6 patients did not meet the inclusion criteria due to a preoperative VAS-A score of zero, and 2 patients had their surgeries deferred. Ultimately, 144 patients were randomized into the study. In the C, R, and E groups, 1 patient from each group was excluded due to surgery time exceeding 2 h. In the RE group, 1 patient was excluded due to conversion to open surgery. As a result, a total of 140 patients were included in the final analysis, with 35 patients in each group.

There was no statistically significant difference between the four groups in terms of gender, age, ASA, height, weight, BMI, educational level, STAI score, duration of surgery, duration of anaesthesia, duration of awakening, and propofol and remifentanil dosages (Table 1).

Compared with group C, VAS-A scores were significantly lower in groups E and RE after admission to the operating room, and in groups R, E, and RE after intravenously injecting remimazolam or normal saline ($P<0.05$). VAS-A scores were significantly lower in groups E and RE after admission to the operating room and in groups R, E, and RE after intravenously injecting remimazolam or normal saline compared with those at the 1 d preoperative visit ($P<0.05$). Ten minutes after receiving either Remimazolam or normal saline, anxiety was observed in 35 (100%), 33 (94%), 35 (100%), and 31 (89%) patients in groups C, R, E, and RE, respectively, as indicated by a VAS-A score greater than zero.

There was no statistically significant difference in VAS-A scores at the 1 d preoperative visit among the four groups (Table 2).

Compared with group C, patients in groups R, E, and RE had a significantly shorter time to first postoperative exhaust and defecation, and significantly lower I-FEED scores ($P<0.05$). The differences in time to first postoperative exhaust and defecation, and I-FEED scores among groups R, E, and RE were not statistically significant. Compared with group C, groups E and RE had significantly higher sleep quality scores on the night before surgery, and groups R, E, and RE had significantly higher sleep quality scores on the first night after surgery and higher patient satisfaction ($P<0.05$). There was no statistically significant difference between the four groups in terms of sleep quality score on the second night after surgery, postoperative Ramsay sedation score, occurrence of postoperative nausea and vomiting, and length of postoperative hospital stay. No adverse reactions such as wound bleeding, infection, or severe abdominal distension occurred in any of the four groups of patients postoperatively (Table 3).

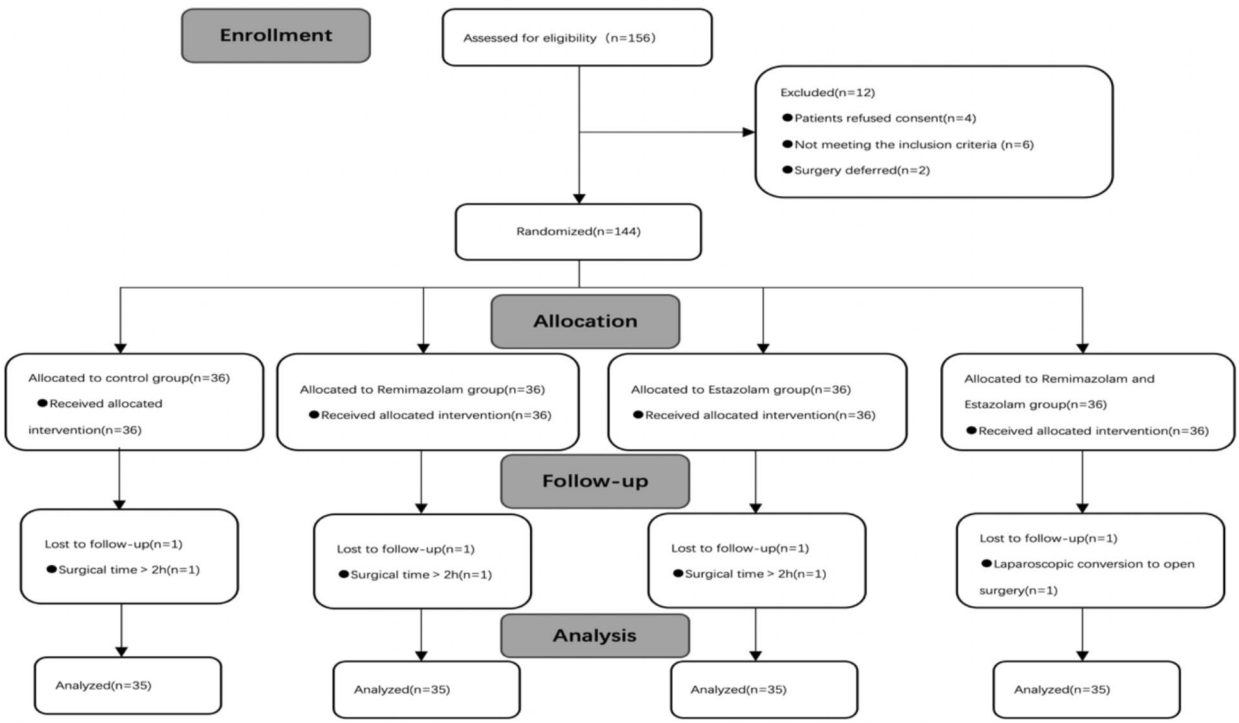

Fig. 1 CONSORT diagram

Table 1 Patient characteristics and intraoperative data ($n=35$)

	Group C	Group R	Group E	Group RE
Gender(F/M)	17/18	16/19	16/19	15/20
Age (years)	45.3 ± 10.5	44.1 ± 11.1	46.4 ± 10.2	46.0 ± 12.4
ASA I/II (*n*)	17/18	18/17	18/17	16/19
Height (cm)	167.7 ± 9.3	169.4 ± 8.1	168.1 ± 8.7	167.7 ± 9.0
Weight (kg)	68.6 ± 12.1	70.3 ± 10.1	68.2 ± 10.2	68.9 ± 11.7
BMI(kg/m^2)	24.2 ± 2.5	24.5 ± 2.6	24.0 ± 2.5	24.3 ± 2.4
Preoperative STAI score				
S-AI	46.2 ± 5.0	47.6 ± 5.3	47.7 ± 4.6	46.5 ± 5.2
T-AI	42.4 ± 3.9	43.6 ± 4.1	42.0 ± 3.8	42.9 ± 3.6
Educational level [*n* (%)]				
Primary school	7 (20.0)	8 (22.9)	9 (25.7)	8 (22.9)
Middle school	18 (51.4)	16 (45.7)	16 (45.7)	15 (42.9)
University and above	10 (28.6)	11 (31.4)	10 (28.6)	12 (34.3)
Duration of surgery (min)	51.5 ± 17.3	49.1 ± 14.9	49.4 ± 14.2	50.3 ± 14.7
Duration of anesthesia (min)	67.2 ± 16.1	65.6 ± 15.8	65.7 ± 17.0	66.8 ± 16.9
Propofol dosage (mg)	338.5 ± 61.2	316.4 ± 56.7	312.3 ± 50.6	322.8 ± 63.4
Remifentanil dosage (μg)	544.6 ± 115.3	518.8 ± 112.5	505.9 ± 118.1	528.4 ± 120.6
Duration of awakening (min)	12.9 ± 4.8	14.2 ± 4.5	12.5 ± 5.0	13.2 ± 4.7

ASA: American Society of Anesthesiologists; BMI: body mass index; STAI: State–trait anxiety inventory; S-AI: State anxiety inventory; T-AI: Trait anxiety inventory

Table 2 VAS-A scores at different timepoints (min, $\bar{x} \pm s$)

Group	*n*	1d preoperative visit	Upon admission to the operating room	10 min after intravenous injection of remimazolam or normal saline
C	35	3.9 ± 1.0	4.2 ± 1.2	4.1 ± 1.2
R	35	3.8 ± 1.1	4.3 ± 1.4	1.9 ± 1.1[ab]
E	35	3.8 ± 1.0	3.2 ± 0.9[ab]	2.8 ± 0.9[ab]
RE	35	3.9 ± 0.9	3.3 ± 1.0[ab]	1.7 ± 0.8[ab]

Group C: Control group; Group R: Remimazolam group; Group E: Estazolam group; Group RE: Remimazolam combined with Estazolam group

Compared with group C

[a] $P<0.05$; compared with 1 d preoperative visit

[b] $P<0.05$

Discussions

Postoperative gastrointestinal dysfunction is a common complication after abdominal surgery, which can be clinically manifested as nausea, vomiting, abdominal distension, delayed exhaustion or defecation, gastrointestinal haemorrhage, and can even cause enterogenic infections and secondary multiorgan dysfunction, which can increase the length of hospital stay and decrease patient satisfaction [10]. Measures to accelerate the recovery of gastrointestinal function generally include optimal perioperative fluid management, early bed mobility and feeding, and implementation of an optimal analgesic programme [11]. Navarro-Tapia et al.'s study showed that anxiety can notably affect different physiological functions of the gastrointestinal tract, such as gastric secretion, intestinal motility, mucosal permeability, and visceral sensitivity, leading to the development of various gastrointestinal disorders [12]. This study demonstrated that patients using remimazolam and estazolam, either alone or in combination, experienced significantly shorter time to first exhaustion and defecation compared to those who did not use these medications. The research also showed that administering estazolam on the night before surgery or remimazolam before the induction of anesthesia, or a combination of both, can be effective in promoting postoperative gastrointestinal function recovery in patients with preoperative anxiety who undergo laparoscopic surgery. In line with our results, Li XR et al. [13] reported that the preoperative anxiety

Table 3 Postoperative gastrointestinal function and other related data

Parameters	Group C	Group R	Group E	Group RE
Time to first exhaust (h)	22.4 ± 5.3	18.7 ± 5.1[a]	18.2 ± 4.6[a]	18.3 ± 4.9[a]
Time to first defecation (h)	43.5 ± 9.7	38.5 ± 7.7[a]	38.2 ± 6.6[a]	37.9 ± 7.0[a]
I-FEED	1 (0 ~ 2)	0 (0 ~ 1) [a]	0 (0 ~ 1) [a]	0 (0 ~ 1) [a]
Ramsay	2(2 ~ 2)	2(2 ~ 2)	2(2 ~ 2)	2(2 ~ 2)
Nausea [*n* (%)]	13 (37.1)	10 (28.6)	9 (25.7)	10 (28.6)
Vomiting [*n* (%)]	9 (25.7)	7 (20.0)	6 (17.1)	6 (17.1)
Sleep quality scores				
One night before surgery	6.1 ± 0.9	5.9 ± 1.2	7.0 ± 1.1[a]	7.2 ± 0.9[a]
The first night after surgery	6.0 ± 1.2	7.1 ± 1.4[a]	6.9 ± 0.9[a]	7.2 ± 1.2[a]
The second night after surgery	7.7 ± 0.9	7.9 ± 0.8	7.8 ± 0.9	7.9 ± 0.9
Patient satisfaction	8 (8 ~ 9)	10 (9 ~ 10) [a]	10 (9 ~ 10) [a]	10 (9 ~ 10) [a]
Length of postoperative hospital stay (d)	4 (3 ~ 4)	3 (3 ~ 4)	3 (3 ~ 3)	3 (3 ~ 4)

I-FEED: intake, feeling nauseated, emesis, physical exam, and duration of symptoms

Compared with group C

[a] $P < 0.05$

state affects postoperative pain scores, as well as prolongs the time to first postoperative exhaustion.

Both remimazolam and estazolam belong to the class of benzodiazepines and possess anxiolytic properties. Remimazolam is a new type of benzodiazepine that has a fast onset, short duration, quick recovery, and no drug accumulation. It is metabolized independently of hepatic and renal function and has few adverse reactions. Remimazolam has the potential to serve as a pre-anaesthetic medication in small doses, effectively mitigating the patient's unease and apprehension upon admission to the operating room [14–16]. Estazolam belongs to the benzodiazepine group with a medium half-life. It is effectively absorbed upon oral administration, and its blood concentration peaks at 2 h on average after oral administration, with 10–24 h of half-life. It is usually used for the treatment of short-term insomnia, anxiety, nervousness, fear, and seizures (Petit Mal and Grand Mal seizures) or preoperative sedation. Oral administration of 1 mg estazolam on the night before surgery can alleviate the tension in patients and improve their sleep quality [17]. This study found no significant difference in patients' awakening time, despite benzodiazepines potentially impacting post-anaesthesia recovery and quality. Gurunathan et al. Error! Reference source not found [18].showed that the addition of benzodiazepines as an adjuvant drug during colonoscopy did not prolong the patients' awakening time or affect the overall quality of recovery. The results of this study are in agreement with this finding. Likewise, Sun et al. [19] showed that preoperative application of remazolam in combination with eszopiclone significantly reduced preoperative anxiety levels in patients undergoing laparoscopic gastrointestinal surgery, facilitated intraoperative hemodynamic stabilization and reduced postoperative pain intensity.

The results of this study showed that there was no statistically significant difference in the time to first postoperative exhaustion and defecation between the remimazolam, estazolam, and combination groups (Figs. 2, 3). The combined use of remimazolam and estazolam theoretically yields a superior anxiolytic effect, thereby enhancing the recovery of gastrointestinal function in the postoperative period. However, the findings of the current study are incongruous with this hypothesis.

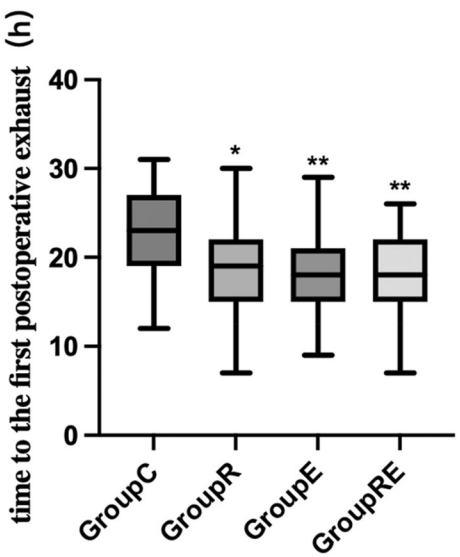

Fig. 2 Time to the first postoperative exhaust, *$p < 0.05$; **$p < 0.01$ vs Group C

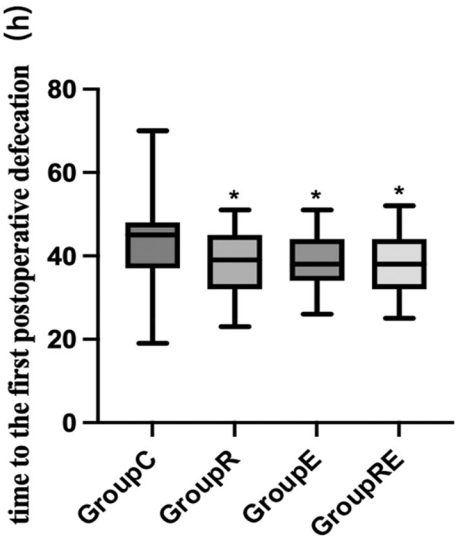

Fig. 3 Time to the first postoperative defecation, *$p < 0.05$ vs Group C

Although two anxiolytics can better relieve patients' anxiety, the combination of the two drugs may weaken gastrointestinal dynamics and does not better promote the recovery of gastrointestinal function. Muller-Lissner et al. [20]demonstrated that intraoperative anaesthesia medication can affect the recovery of gastrointestinal function directly or indirectly.

The central nervous system has a strong correlation with gastrointestinal function, and prolonged periods of anxiety may lead to gastrointestinal symptoms, such as indigestion, diarrhoea, or abdominal pain. The brain communicates with the gut through multiple pathways, including the autonomic nervous system, the hypothalamic–pituitary–adrenal axis, and the immune system, which are collectively referred to as the brain–gut axis (BGA) [21]. In addition, the dysregulation of BGA can be induced by anxiety, thereby resulting in various intestinal disorders, and influencing the recuperation of gastrointestinal function after surgery. In addition, disturbances in the composition of the gut microbiota have been associated with anxiety and depression, and psychological stress may lead to microbiota translocation, which in turn exacerbates intestinal inflammation [22]. Stress can lead to a reduction in certain intestinal epithelial tight junction proteins, which can compromise the integrity of the intestinal epithelium. This can cause changes in intestinal motility, affect secretion and mucoprotein production, and ultimately result in changes in microbial composition and intestinal permeability. These changes can further impact gastrointestinal function [23].

Furthermore, according to this study, patients who took a single estazolam or remimazolam, or a combination of both drugs, experienced significant improvement in their sleep quality on the night before their surgery. Similarly, patients who received either drug alone or in combination also reported a significant enhancement in their sleep quality on the first night after the surgery. The administration of estazolam and remimazolam prior to surgery has been proven to be efficacious in enhancing the sleep quality of the patients, regardless of the presence of any other factors that may have influenced it. Poor sleep quality is associated with gastrointestinal symptoms and poor nighttime sleep can lead to the exacerbation of gastrointestinal symptoms the following day [24, 25]. A review indicated that sleep disruption activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) [26]. Activation of β-adrenergic signaling leads to the expression of inflammatory genes, the production of pro-inflammatory cytokines, and the increase in systemic inflammatory markers, such as IL-6 and TNF-α [27]. Research has shown that in elderly individuals with poor sleep quality, there is an increased expression of IL-6 and TNF-α [28]. TNF-α has been shown to increase intestinal epithelial cell shedding and apoptosis, induce changes in tight junction morphology, and alter intestinal permeability, thereby exacerbating intestinal inflammation [29]. Caroline Zhao et al. [28]showed that good sleep quality during the perioperative period in patients undergoing abdominal surgery contributes to their postoperative recovery of gastrointestinal function, which is consistent with our research results. The concept of comfortable medical treatment has gained attention among anaesthesiologists and surgeons, leading to the increased focus on the sleep of hospitalized patients before and after surgery. Administering an appropriate dosage of benzodiazepines before surgery can effectively reduce psychological stress, improve the quality of sleep, and provide a solid foundation for preoperative preparation and postoperative recovery.

There are some shortcomings in this study. First, the study only demonstrates that preoperative administration of Remimazolam, Estazolam, or their combination can reduce preoperative anxiety levels and promote postoperative gastrointestinal recovery. While the study suggests that reducing preoperative anxiety may be associated with postoperative gastrointestinal recovery, it does not establish a causal relationship between the two. Future studies should expand the sample size and conduct subgroup analyses to explore the relationship between preoperative anxiety and postoperative gastrointestinal function. Second, the sample size was small and might be biased. Third, this study mainly focused on patients undergoing laparoscopic cholecystectomy surgery, which is a relatively low-risk procedure, and the results of the study are not necessarily applicable to

high-risk surgical patients. Fourth, it is yet to be confirmed whether similar outcomes can be observed with other anxiolytic medications as this study exclusively focused on benzodiazepines. Finally, support from objective indicators of gastrointestinal function such as gastrin and intestinal fatty acid binding protein (I-FABP) is absent, and further validation is required in the future.

In conclusion, preoperative application of remimazolam or estazolam separately or in combination, can effectively alleviate the preoperative anxiety state of patients undergoing laparoscopic cholecystectomy surgery and accelerate the postoperative recovery of gastrointestinal function. In addition, the combined administration of these two drugs can improve the quality of the patients' sleep on the night before surgery and increase patient satisfaction.

Author contributions
Mao was responsible for conducting the experiments and drafting the initial manuscript. Gao and Huang were in charge of data collection. He carried out data analysis. Yao was responsible for the creation of the figures. All authors have reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the Ethics Committee of the First People's Hospital of Lianyungang. All participants were informed about the study, and written informed consent was obtained from them. All methods were carried out in accordance with relevant guidelines and regulations.

Competing interests
The authors declare no competing interests.

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