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Effect of improving sleep quality the night before surgery with zolpidem on postoperative gastrointestinal function in patients undergoing laparoscopic partial colorectal resection: a randomized, double-blind, controlled trial

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Abstract

Background Sleep is one of the basic physiological needs of human beings. Preoperative sleep disorders are associated with poor prognosis in surgical patients, and sleep disorders have been shown to be one of the risk factors for gastrointestinal dysfunction. However, there are now few studies to investigate whether improving preoperative sleep disorders can promote the recovery of postoperative gastrointestinal function. This study aimed to investigate the effects and significance of improving preoperative sleep quality with zolpidem on postoperative gastrointestinal function.

Methods In this prospective, randomized, double-blind clinical trial, 76 patients undergoing elective laparoscopic partial colorectal resection and with a Pittsburgh Sleep Quality Index (PSQI) score > 5, were randomly divided into two groups. The zolpidem group (Group Z, $n = 38$) was given a capsule containing 10 mg of zolpidem the night before the operation, and the control group (Group C, $n = 38$) was given an empty capsule the night before the operation. Follow-up visits were performed on the 1st, 3rd, and 7th postoperative days, respectively. The primary outcome of this study was the I-FEED (Intake, Feeling nauseated, Emesis, Physical Exam, and Duration of symptoms) score on the third postoperative day (POD3). Secondary outcomes included time to postoperative first flatus, first feces, and first food intake (semi-liquid diet), I-FEED scores, visual analog scores (VAS) during coughing and at rest, times of patient-

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controlled intravenous analgesia (PCIA) effective presses, sufentanil dosage, number of remedial analgesia in the 24-hour postoperative period, and changes in inflammatory markers (TNF-α).

Results Compared with Group C, Group Z had a lower I-FEED score on POD1 ($P < 0.05$) and shorter time to first flatus and first food intake ($P < 0.05$); there were significant differences between the two groups in VAS scores during coughing and at rest on POD1, VAS score during coughing on POD3, times of PCIA effective presses and sufentanil dosage in the 24-hour postoperative period, and patient satisfaction ($P < 0.05$).

Conclusion For patients with sleep disorders, the use of zolpidem to improve sleep the night before surgery is beneficial in partially improving postoperative gastrointestinal function, relieving postoperative pain, and increasing patient satisfaction.

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Keywords Preoperative sleep disorders, Postoperative gastrointestinal function, Zolpidem, Inflammation response, Laparoscopic partial colorectal resection

Introduction

Colorectal cancer is the fourth most deadly cancer in the world, with approximately 900,000 deaths annually, accounting for about 10% of all cancers and cancer-related deaths diagnosed globally each year. Moreover, the incidence of colorectal cancer continues to rise in developing countries. The incidence of colorectal cancer is projected to increase to 2.5 million new cases worldwide by 2035 [1]. Laparoscopic partial colorectal resection is the mainstream treatment for colorectal cancer [2]. Although laparoscopic surgery has the advantages of less trauma and less pain compared with traditional open surgery [3], the effect of carbon dioxide artificial pneumoperitoneum on the physiological function of the patient during laparoscopic surgery cannot be ignored. Artificial pneumoperitoneum can not only cause significant stress reactions in the body, but also have different degrees of impact on postoperative gastrointestinal function. Postoperative ileus (POI) is a manifestation of impaired gastrointestinal function, which is a transient cessation of peristalsis after intestinal resection that prevents efficient transportation of intestinal contents and reduces the tolerance of dietary intake. Patients suffer not only mentally from gastrointestinal dysfunction but also physically due to the pain caused by complications and prolonged postoperative hospitalization [4]. Therefore, it is particularly important to promote the recovery of gastrointestinal function after surgery.

Sleep disorders are defined as clinically significant disturbance in either the quantity, the quality or rhythm of sleep, wakefulness, or the wake-sleep cycle that occurs in an individual [5]. According to the World Health Organization, 27% of the world's population suffers from sleep disorders. Data from the China Sleep Research Society shows that as many as 300 million Chinese have sleep disorders, with a prevalence rate of 38.2% in adults. Chronic sleep disorders may lead to cognitive dysfunction, prolong postoperative recovery time, and increase the risk of postoperative complications [6]. In addition, it has been found that sleep quality may affect gastrointestinal function through brain-gut axis mechanisms. Specifically, sleep disorders can lead to elevated inflammatory factors in the body, as well as disturbances in the intestinal flora, and the imbalance between pro-inflammatory and anti-inflammatory factors can also exacerbate oxidative stress [7], which can affect gastrointestinal function [8–10]. Currently, there are articles confirming the interaction between GI dysfunction and sleep disorders [11], and based on this, melatonin has also been proposed as an adjunctive treatment for gastrointestinal dysfunction [12, 13]. However, no studies have been conducted to investigate whether improving preoperative sleep disorders can promote the recovery of gastrointestinal function after surgery. Therefore, the aim of this study was to investigate the effect of improving sleep quality with zolpidem the night before surgery on postoperative gastrointestinal function, expecting to help clinicians provide such patients with individualized interventions as early as possible in the perioperative period, to improve the quality of postoperative recovery, and to promote rapid postoperative recovery.

Methods

Study design

This double-blind, prospective, randomized, controlled study was conducted at the First People's Hospital of Lianyungang. The trial was approved by the Ethics Committee of the First People's Hospital of Lianyungang (KY-20231004002-02) and registered in the China Clinical Trial Registry (ChiCTR2300077566). Eighty-six patients who underwent elective laparoscopic partial colorectal resection under general anesthesia from November 2023 to August 2024 at the First People's Hospital of Lianyungang were chosen in this study.

The main inclusion criteria were: patients diagnosed primary colorectal carcinoma and with Pittsburgh Sleep Quality Index (PSQI) score > 5, age 18–80 years old, body mass index (BMI) 18–35 kg/m^2, the American Society of

Anesthesiologists (ASA) class I–III, patients who were tolerant to the drugs in this study, and those who voluntarily participated in this study and signed the informed consent. Patients who met one of the following criteria were excluded: history of oral sedation and analgesia within 14 days before surgery; sleep apnea, drug allergy, drug abuse, combination of severe cardiac, brain, renal, pulmonary, and hepatic impairments or other malignant neoplastic diseases, history of psychoneurological disorders; severe hearing impairment or inability to understand or complete the Pittsburgh sleep quality index (PSQI) questionnaire; refusal to participate in the trial. Written informed consent was obtained from all recruited patients or their authorized family members.

Randomization and blinding

Randomization was performed using a secure web-based system. Based on a computer-generated randomization sequence, patients were divided into two groups, the zolpidem group (Group Z) and the control group (Group C). We kept the grouping information in an opaque envelope sealed, then placed 10 mg of zolpidem in a capsule and assigned a nurse not involved in the study to give zolpidem to patients in Group Z at bedtime and the empty capsule to patients in Group C at bedtime. Thus, the patients were not aware of the grouping. Clinical information collectors, data analysts, surgeons, anesthesiologists, nurses administering medications, and other health care.

personnel were blinded to the grouping.

Methods of intervention

An anesthesiologist not involved in the surgery assessed each patient's sleep quality the day before surgery using the PSQI, which all patients participating in the trial were asked to complete independently. The PSQI scale was designed by Buysse et al. It consists of 18 items in 7 sections, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, use of sleeping pills, and daytime dysfunction. The scale assesses the subject's sleep quality over the last month, with higher scores on the test indicating poorer sleep quality. A score of 5 is an empirically determined cut-off point [14].

All subjects were assessed by an anesthesiologist, unaware of the grouping, for sleep quality the night before surgery using the Leeds Sleep Evaluation Questionnaire (LSEQ) upon entering the operating room. The LSEQ questionnaire consists of 10 questions covering 4 areas: the ease of getting to sleep (GTS, items 1–3), the quality of sleep (QOS, items 4 and 5), awakening from sleep (AFS, items 6 and 7), and behavior following wakefulness (BFW, items 8–10) [15]. The LSEQ questionnaire allows for a multifaceted assessment of the effects of pharmacological interventions on sleep over a short period of time [16]. Patients' anxiety levels were also assessed using the Visual Analog Scale for Anxiety (VAS-A), which has been shown to be a reliable indicator for assessing preoperative anxiety [17].

The postoperative management protocol included encouraging the patient to sit up and mobilize out of bed as early as possible four hours after the surgery. On the first postoperative day, patients were advised to begin with water intake. Depending on their tolerance, the diet was progressively advanced from liquids to semi-liquids and eventually to solid foods. Intravenous fluid infusion was discontinued as early as feasible based on oral feeding recovery. Additionally, the urinary catheter was removed on the first postoperative day, with careful monitoring of urinary output.

Methods of anesthesia

All patients were required to fast for 8 h and abstain from drinking for 2 h before surgery. Upon the patient's admission 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. After Allen's test, radial arterial puncture cannulation was performed and invasive blood pressure was measured.

Anesthesia was induced with sufentanil 0.3 μg/kg, propofol 2 mg/kg, and vecuronium bromide 0.1 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 (1.5–6 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and propofol (4–10 $mg \cdot kg^{-1} \cdot h^{-1}$) were used for maintenance of general anesthesia by a syringe pump to maintain bispectral index (BIS) at 40–60. To maintain muscle relaxation, vecuronium bromide 0.03 mg/kg was administered as needed intravenously. When blood pressure and heart rate fluctuated out of a range of 20% of the basal level, vasoactive drugs were used for adjustment.

All patients received intravenous sufentanil 0.1 μg/kg and acetaminophen mannitol injection 500 mg 30 min before the end of surgery to prevent postoperative pain, as well as intravenous dolasetron mesylate 12.5 mg and dexamethasone 10 mg to prevent postoperative nausea and vomiting. Propofol and remifentanil were discontinued while stitching the skin. The endotracheal tube was removed when the indications for extubation were met, and then the patients were admitted to the post-anesthesia care unit. Ramsay sedation score was measured 30 min after extubation, and patients were transferred to the ward when the relevant standard was met.

A patient-controlled intravenous analgesia (PCIA) pump was used postoperatively. The analgesic pump formulation was 2 μg/kg of sufentanil and 100 mg of dolasetron, with a total fluid volume of 100 mL. The analgesic pump infusion rate was 2 mL/h, and the self-administered dose was 1.5 mL.

Clinical data collection

Clinical data were collected by an anesthesiologist who was unaware of grouping. Preoperative demographic characteristics of the patients were collected, including gender, age, BMI, past medical history, ASA classification, PSQI score, and LSEQ score. Intraoperatively, mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were recorded upon admission to the operating room, after anesthesia induction, at the time of skin incision, at the end of the procedure, and after extubation; intraoperative medications, anesthesia, length of surgery, and surgical complications were also recorded.

Patients were followed up on days 1, 3, and 7 postoperatively and the number of PCIA effective press times and sufentanil dosage in the 24-hour postoperative period, as well as the number of times of remedial analgesia, the intake, feeling nauseated, emesis, physical examination, and duration of symptoms (I-FEED) scores and visual analog scores (VAS) (with a score of 0 for no pain and a score of 10 for maximal pain) during coughing and at rest on these three days were recorded. The I-FEED scoring system assigns 0 to 2 points for each of 5 components, which include intake, feeling nauseated, emesis, physical examination, and duration of symptoms, then categorizes patients as having normal gastrointestinal function (scores of 0–2), postoperative gastrointestinal intolerance (scores of 3–5), or postoperative ileus (scores of ≥ 6) [18]. The time to postoperative first flatus, first feces, and first food intake (semi-liquid diet), as well as the occurrence of postoperative complications were also recorded.

Whole blood specimens (approximately 4 mL) were collected from patients using serum separator tubes on the day before surgery (T0), before anesthesia induction (T1), immediately after the operation (T2), and 24 h after surgery (T3). The blood samples were left at room temperature for 2 h, centrifuged at 1000 × g for 15 min, and then the supernatants were stored at − 80 °C. Serum concentrations of TNF-α were measured by enzyme-linked immunosorbent assay (ELISA).

Outcome measures

The primary outcome was the I-FEED score of POD 3. Secondary outcomes included preoperative demographic characteristics of the patients including gender, age, BMI, past medical history, ASA classification, PSQI score and LSEQ score, MAP and HR upon admission to the operating room, intraoperative medications, anesthesia, length of surgery and surgical complications, the time to postoperative first flatus, first feces and first intaking, the occurrence of postoperative complications and pain scores, I-FEED score and serum TNF-α concentrations at different time points.

Statistical analysis

Before this study, a preliminary study was conducted on each of the two groups to determine the sample size. The primary outcome of this study was the I-FEED score of POD 3. Based on the pre-test results, the I-FEED score of POD 3 in Group Z is 4.0 ± 0.632 ($n = 6$), and the I-FEED score of POD 3 in Group C is 4.5 ± 0.837 ($n = 6$). And G*power 3.1 statistical software was applied to calculate sample size. Based on 80% power, $\alpha = 0.05$ and Cohen´s d effect size = 0.674, a total of 72 patients were needed. We anticipated a 20% dropout rate in patients, and given the 1:1 ratio, 86 patients were ultimately enrolled in the study.

The SPSS 25.0 statistical software was applied for analysis. A total of 76 patients in this trial could be evaluated for the per-protocol analysis. Shapiro-Wilk test was used to analyze the normality of the variables, and the measurement data conforming to normal distribution were expressed as mean ± standard deviation (x ± s), with the t-test used for comparison between groups. The data not conforming to normal distribution were described by median and quartiles, and a non-parametric test was used for comparison between groups. Count data were expressed as rates and the X^2 test was used for comparison between groups, while the rank-sum test was used for rank data. $P < 0.05$ is considered as a statistically significant difference.

Results

A total of 120 patients were screened for participation in the trial, and 34 patients were excluded according to the inclusion criteria. After enrollment, 10 patients were eliminated, including 3 patients with data loss during follow-up, 5 patients who were transferred to the ICU postoperatively, and 2 patients who were converted to open surgery during the procedure. Thus, a total of 76 patients were finally included in the trial and randomized into 2 groups: the control group (Group C, $n = 38$) and the zolpidem group (Group Z, $n = 38$) (Fig. 1).

Abbreviations: Group C, control group; Group Z, zolpidem group; ICU, Intensive Care Unit.

Demographic data such as age, gender, BMI, ASA classification, type of surgery, past medical history, and PSQI score were similar in both groups. In addition, there were no significant differences in intraoperative data, intraoperative medications, intraoperative fluid intake and

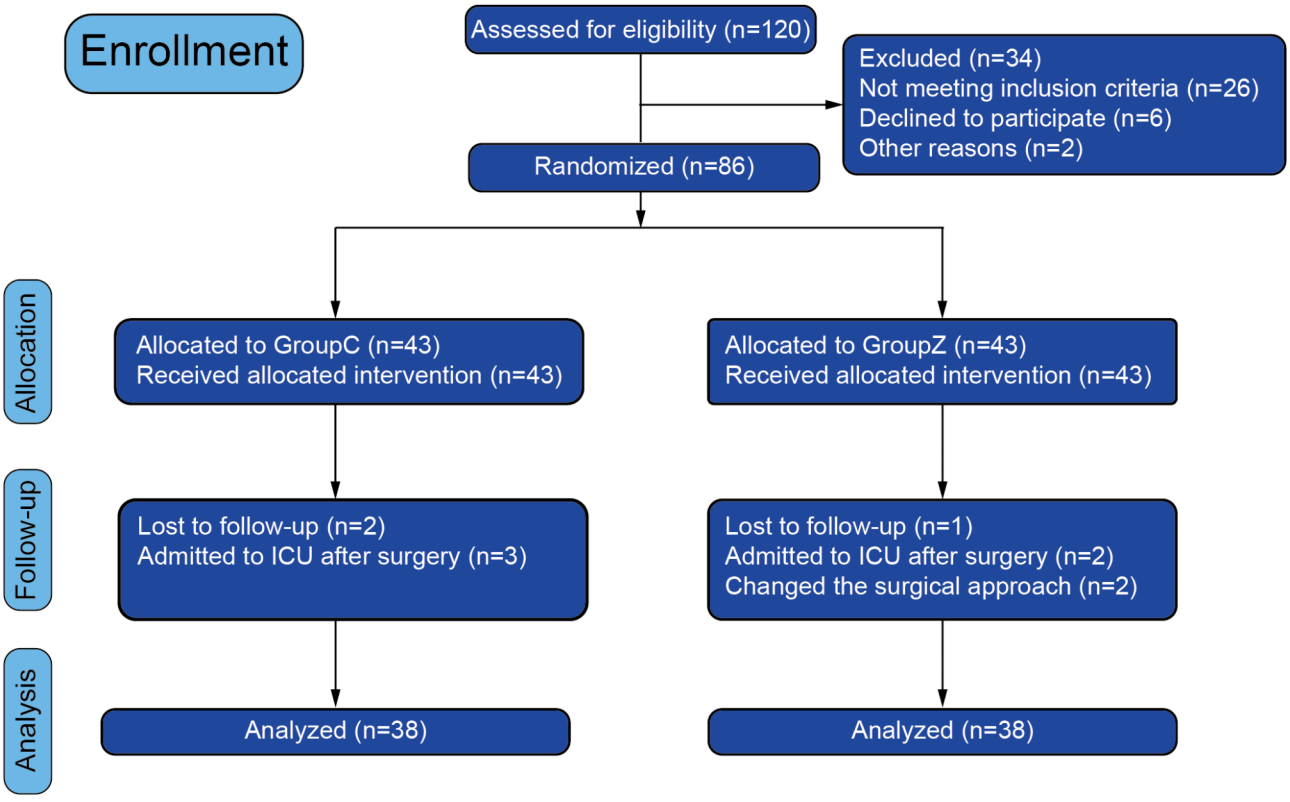

Fig. 1 CONSORT flow diagramfor the study

output, and other parameters between the two groups (Table 1).

The LSEQ scores on the night before surgery and the VAS-A scores after entering the operating room are shown in Table 2. Group Z's ease of getting to sleep and sleep quality scores were significantly better than those of Group C. However, there was no significant difference between the two groups in terms of awakening and behavior following wakefulness. Group Z's VAS-A score was significantly lower than that of Group C after entering the operating room.

The postoperative I-FEED scores are shown in Table 3. The I-FEED score on POD1 in Group Z was 4 (1), lower than in Group C (5 [2]; $P=0.001$). As for the I-FEED scores on POD3 and POD7, there was no difference between the two groups.

Table 4 shows the comparison of VAS scores at rest and during coughing between the two groups. At any time point, VAS scores were lower in Group Z than in Group C. On POD1, patients in Group Z had lower VAS scores compared to Group C (resting: 2 [1] vs. 3 [1]; $P<0.01$, coughing: 4.5 [1] vs. 5 [0.25]; $P<0.05$). On POD3, patients in Group Z had lower VAS scores during coughing compared to Group C (3 [1] vs. 4 [1]; $P<0.001$). However, the difference between the groups at rest was not significant ($P=0.141$). There was also no statistically significant difference in VAS scores at rest and during coughing between the two groups on POD7 (rest: $P=0.089$, coughing: $P=0.158$).

There was no difference in the baseline data of TNF-α at T0 between the two groups. At T1, T2, and T3, the TNF-α values in Group Z were smaller than those in Group C. However, the difference was statistically significant only at T3 (5.68 ± 1.69 vs. 6.99 ± 3.26; $P=0.031$), and the difference was not statistically significant at the remaining time points. (Table 5)

Table 6 documents the postoperative follow-up. According to patient self-report, the median time to first flatus (63.5 [22.75] vs. 74 [24.5], $P=0.010$) and the median time to first intaking (121 [16.75] vs. 130 [19.25], $P=0.021$) were significantly lower in Group Z than in the control group. The patient satisfaction was also higher in Group Z ($P=0.008$). In terms of postoperative analgesia, on the first postoperative day, the times of effective press with the PCIA (1 [1] vs. 2 [1], $P=0.000$) and the consumption of sufentanil (64.21 ± 8.78 vs. 68.12 ± 8.01, $P=0.046$) were significantly reduced in Group Z compared with Group C. There were no significant differences between the two groups in terms of postoperative complications, length of hospitalization,30 readmission rate, and rescue analgesia.

Table 1 Basic information and surgical data

	Group C	Group Z	χ^2/Z/t	*P*
Age (yr)	65(9.5)	66(12.25)	-0.016	0.988
Gender				
Male	22(57.9%)	23(60.5%)	0.054	0.815
Female	16(42.1%)	15(39.5%)		
BMI (kg/m^2)	24.20 ± 2.68	24.22 ± 2.67	-0.027	0.979
ASA				
I	0	0		
II	30(78.9%)	31(81.6%)	0.083	0.773
III	8(21.1%)	7(18.4%)		
Incision				
Non-stoma	29(76.3%)	30(78.9%)	0. 076	0.783
Stoma	9(23.7%)	8(21.1%)		
Comorbidities				0.697
Hypertension	9(23.7%)	10(26.3%)		
Diabetes mellitus	3(7.9%)	5(13.2%) 0.769		
None	26(68.4%)	23(60.5%)		
Pulse rate	76(14)	77.5(16.5)	-0.946	0.344
MAP	100.32 ± 10.87	96.29 ± 10.37	0.442	0.103
Duration of surgery (min)	159.68 ± 45.59	157.74 ± 42.77	0.192	0.848
Time of extubation (min)	14.11 ± 5.90	11.82 ± 4.83	1.851	0.068
Perioperative medications				
Propofol (mg)	130(20)	140(30)	-1.391	0.164
Sufentanil (μg)	26(3.5)	28(5)	-1.587	0.112
Vecuronium bromide (mg)	7(1)	7(1.25)	-1.442	0.149
Remifentanil (mg)	0.741 ± 0.162	0.667 ± 0.158	-1.867	0.062
Norepinephrine (μg)	2(23)	6(16)	-0.814	0.416
Ephedrine (mg)	0(0)	0(0)	-0.015	0.988
Atropine (mg)	0(0)	0(0)	0.000	1.000
Esmolol (mg)	0(0)	0(0)	0.000	1.000
Infusion volume (mL)	2000(500)	2225(500)	-0.214	0.830
Blood volume (mL)	100(142.5)	100(150)	-0.473	0.636
Urine volume (mL)	300(100)	200(162.5)	-0.21	0.834
PSQI scores	10(2)	10(3)	-0.582	0.560

Notes: Values are mean ± SD, number (%) and median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; Group C, control group; Group Z, zolpidem group; MAP, mean arterial pressure; PSQI, Pittsburgh sleep quality index

Table 3 Postoperative I-FEED scores

	Group C	Group Z	Z	*P*
POD1	5(2)	4(1)	-3.257	0.001*
POD3	5(1)	4(1)	-1.236	0.217
POD7	2(0.25)	2(0)	-1.575	0.115

Notes: Values are median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: Group C, control group; Group Z, zolpidem group; I-FEED, intake, response to nausea treatment, emesis, exam, and duration; POD 1, the first postoperative day; POD 3, the third postoperative day; POD 7, the seventh postoperative day

Table 2 LSEQ and VAS-A scores

	Group C	Group Z	Z/t	*P*
GTS	47.34 ± 4.65	74.32 ± 7.18	19.433	0.000**
QOS	46.16 ± 5.91	73.68 ± 7.84	17.281	0.000**
AFS	54.47 ± 2.45	55.34 ± 2.27	1.604	0.113
BFW	55.000(3.0)	55.000(4.0)	-0.671	0.502
VAS-A	4.000(1.0)	4.000(1.0)	-3.530	0.000**

Notes: Values are mean ± SD and median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: AFS, awakening from sleep; BFW, behavior following wakefulness; Group C, control group; Group Z, zolpidem group; GTS, the ease of getting to sleep; LSEQ, Leeds sleep evaluation questionnaire; QOS, the quality of sleep; VAS-A, visual analog scale for anxiety

Table 4 Postoperative VAS scores

	Group C	Group Z	Z	*P*
POD1, coughing	5(0.25)	4.5(1)	-2.434	0.015*
POD1, rest	3(1)	2(1)	-2.848	0.004*
POD3, coughing	4(1)	3(1)	-4.338	0.000**
POD3, rest	2(1)	1(1)	-1.472	0.141
POD7, coughing	3(1)	2(1)	-1.41	0.158
POD7, rest	0.5(1)	0(1)	-1.699	0.089

Notes: Values are median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: Group C, control group; Group Z, zolpidem group; POD 1, the first postoperative day; POD 3, the third postoperative day; POD 7, the seventh postoperative day; VAS, visual analog scores

Table 5 Serum TNF-α-concentrations

	Group C	Group Z	t	*P*
T0 (pg/mL)	4.98 ± 2.62	4.99 ± 1.99	0.008	0.994
T1 (pg/mL)	5.12 ± 2.73	4.89 ± 1.93	-0.428	0.670
T2 (pg/mL)	7.87 ± 3.37	6.93 ± 2.30	-1.421	0.160
T3 (pg/mL)	6.99 ± 3.26	5.68 ± 1.69	-2.209	0.031*

Notes: Values are mean ± SD. * $P < 0.05$, ** $P < 0.01$

Abbreviations: Group C, control group; Group Z, zolpidem group; T0, the day before surgery; T1, before induction of anesthesia; T2, the immediate postoperative period; T3, 24 h after surgery

Discussions

This randomized controlled trial investigated the effect of improving preoperative sleep quality with zolpidem on the recovery of gastrointestinal function in patients undergoing laparoscopic partial colorectal resection. The results of this study showed that the zolpidem group had a shorter time to first flatus and food intake and lower I-FEED score on the first postoperative day compared to the control group, but no statistically significant differences were found in postoperative gastrointestinal function as measured by the I-FEED scores on the third postoperative day and the seventh postoperative day. In addition, pain scores on the first postoperative day and patient satisfaction were significantly better in the zolpidem group than in the control group.

With the development of medical technology, the current status of rapid perioperative recovery of patients has received increasing attention. The concept of ERAS (Enhanced Recovery After Surgery) is to promote the postoperative recovery of patients by alleviating the

Table 6 Postoperative outcomes

	Group C	Group Z	χ^2/Z/t	*P*
Sufentanil consumption (ug)	68.12 ± 8.01	64.21 ± 8.78	2.027	0.046*
PCIA effective press times	2(1)	1(1)	-4.435	0.000**
Rescue analgesia	0(1)	0(0)	-0.897	0.370
Time to first feces (h)	97.21 ± 19.34	89.76 ± 18.35	1.722	0.089
Time to first flatus (h)	74(24.5)	63.5(22.75)	-2.578	0.010*
Time to first intaking (h)	130(19.25)	121(16.75)	-2.313	0.021*
Patient satisfaction	8(1)	9(1)	-2.643	0.008*
Length of stay	16(3.5)	16(3)	-0.679	0.497
30 readmission rate				
Not hospitalized	24(63.2%)	19(50.0%)	1.339	0.247
Hospitalization	14(36.8%)	19(50.0%)		
Complications				
None	32(84.2%)	31(81.6%)	0.093	0.761
Fever	6(15.8%)	7(18.4%)		

Notes: Values are mean ± SD, number (%) and median (IQR). * $P < 0.05$, ** $P < 0.01$

Abbreviations: Group C, control group; Group Z, zolpidem group; PCIA, patient-controlled intravenous analgesia

stress caused by surgical trauma and other management measures. Rapid recovery of gastrointestinal function after surgery is a key element of ERAS [19], and it is gaining more attention from surgeons and anesthesiologists. Sleep is one of the basic physiological needs of humans, and sleep disorders affect a large number of patients undergoing surgery, which can adversely affect their recovery. One study reported that nearly 40% of colorectal cancer patients in China had preoperative insomnia [20]. Therefore, in order to promote the rapid recovery of patients after surgery, we should also pay more attention to the preoperative sleep quality of surgical patients, which is in line with the recent European guidelines on the preoperative assessment of adults undergoing elective noncardiac surgery that emphasize the importance of comprehensive preoperative assessment and optimization to improve surgical outcomes [21].

The sleep aid used in this study was zolpidem, a non-benzodiazepine hypnotic that belongs to a new class of psychotropic drugs called imidazopyridines. It enhances the $GABA_A$ receptor by selectively binding to omega-1 receptor subtypes [22]. Zolpidem is a proven safe and effective drug characterized by rapid onset of action and minimal drug residuals and rebound effects. In clinical applications, zolpidem is used to treat transient episodic insomnia and chronic insomnia by increasing the ratio of rapid eye movement (REM) sleep to slow-wave sleep (SWS) to repair sleep disruption [23, 24]. Its side effects include ataxia or poor motor coordination and difficulty in maintaining balance. It has been shown that the side effects of zolpidem are related to the dose used, which is commonly associated with the use of more than 20 mg per day [22]. In contrast, in this trial, only a single 10mg [25–27] (It is also the recommended dose in the drug description.) was given and the LSEQ scores showed no significant difference in AFS and BFW between the two groups, so statistically no relevant side effects were found.

Most of the primary outcomes in previous studies of perioperative use of zolpidem to improve sleep quality were postoperative pain. Types of surgery include hip and knee replacements [26], knee arthroscopy [28], rotator cuff repair [29], spine surgery [30], and laparoscopic partial colorectal resection [31]. These articles suggest that improved sleep with pre- or postoperative use of zolpidem reduces postoperative pain and decreases postoperative opioid use. Our study yielded similar results. There are also articles stating that the use of rescue analgesia can be reduced, which is inconsistent with the results of our study.

A study confirmed a significant relationship between sleep disturbances and gastrointestinal symptoms, including epigastric discomfort, nausea, dysphagia, reflux symptoms, diarrhea, and constipation [32]. Poor nighttime sleep can lead to worsening gastrointestinal symptoms the following day [33]. These gastrointestinal symptoms may be associated with an inflammatory response due to sleep disorders. A review has indicated that sleep disorders are associated with systemic inflammatory responses [34] and that sleep disruption activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). In particular, the activation of β-adrenergic signaling induces an increase in nuclear factor κB (NF-κB), inflammatory gene expression, pro-inflammatory cytokine production, and systemic inflammatory markers [35, 36]. In addition to this, studies have confirmed that normal nighttime sleep is associated with decreased sympathetic excitability [37]. Whereas, abnormal sleep leads to abnormal sustained activation of sympathetic pathways, which could plausibly explain the correlation between sleep disorders and inflammatory markers. These inflammatory markers include tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and nitric oxide (NO). Tumor necrosis factor (TNF) plays a central role in coordinating the inflammatory response in mammals [38]. It also plays a key role in maintaining intestinal integrity and has been implicated in the pathogenesis of intestinal inflammation [39]. TNF-α has been shown to increase intestinal epithelial cell shedding and apoptosis, and to induce changes in tight junction morphology and intestinal permeability [40, 41]. In addition, TNF-α-mediated signaling plays an important role in maintaining the colonic epithelial barrier and wound healing [39]. In summary, lower levels of postoperative TNF-α may be able to promote the

recovery of gastrointestinal function, which needs to be confirmed by further studies. Our results showed that improved sleep resulted in lower levels of TNF-α, lower I-FEED scores, and shorter time to postoperative first flatus and first food intake on POD1 compared with the control group. Interestingly, we found that improved sleep quality favored patients' recovery of postoperative gastrointestinal function.

The results of this trial showed that improved preoperative sleep relieved pain on POD1 and reduced the use of sufentanil in the analgesic pump, a result similar to that of a randomized controlled trial [31]. Opioids are one of the most commonly used analgesics for the treatment of acute postoperative pain and mediate their effects mainly through interactions with three G-protein-coupled receptors: μ-opioid receptors, δ-opioid receptors, and κ-opioid receptors, which are expressed by central and peripheral (including intestinal) neurons. It has been found that chronic stimulation of μ-opioid receptors may be involved in esophageal motility disorders and is associated with sphincter of Oddi dysfunction. The κ-opioid receptors mediate responses such as analgesia, sedation, and bowel dysfunction. Although δ-opioid receptors are mainly localized in the central nervous system and mediate analgesia and respiratory depression, they are also present in the intermuscular plexus and submucosal plexus of the intestines, exerting inhibitory effects on gastrointestinal motility and secretion [42]. Therefore, a decrease in opioid use after surgery may have a certain effect on the recovery of gastrointestinal function.

In addition, this study found that improved sleep the night before surgery was effective in relieving patient anxiety, and it has been demonstrated that preoperative anxiety delays the recovery of postoperative gastrointestinal function. Anxiety leads to the activation of the HPA axis and an increase in the body's stress response; it also causes dysregulation of the brain-gut axis, which leads to different intestinal disorders and affects the recovery of gastrointestinal function in the postoperative period. Kim et al. found that the application of buspirone in mice significantly suppressed stress-induced anxiety or depression behaviors and altered the composition of the intestinal microbiota of the mice [43]. Besides, anxiety may lead to a shift in gut flora, which can worsen intestinal inflammation. It may also reduce specific intestinal epithelial tight junction proteins in the intestinal epithelium, compromising its integrity. This disruption can affect intestinal motility and lead to alterations in microbial composition and intestinal permeability [44, 45].

The statistical results of this trial showed that the difference in I-FEED scores on POD3 between the two groups was not statistically significant, but the difference in I-FEED scores on POD1 was statistically significant. We speculated several reasons for this. First, as discussed previously, TNF-α values can have an effect on gastrointestinal function, and the difference in serum TNF-α values on POD 1 between the two groups was statistically significant. However, due to the limitation of conditions, our protocol did not collect blood samples from patients on POD 3. Future studies could consider collecting such data to supplement the lack of evidence. Secondly, there was a significant difference in pain scores between the two groups on POD1, whereas there was little difference in pain scores on POD3. There is evidence that the gut microbiome is associated with the development of postoperative pain [46], which may affect the recovery of gastrointestinal function. Finally, since this was a single-center, small-sample trial, the results were susceptible to some individual differences. This suggests that future studies with large sample sizes are needed for further validation.

There are some limitations in this study. First, this trial did not use objective indicators such as polysomnography to monitor sleep, nor did it differentiate between types of sleep disorders, which may have varying effects on gastrointestinal function. Second, due to the lack of uniform criteria for assessing postoperative gastrointestinal function, only the I-FEED score and conventional gastrointestinal function indicators were used for validation, and future studies are needed to establish more reliable assessment indicators to assess the recovery of gastrointestinal function. Third, the sample size of this trial was relatively small. Fourth, in order to maintain the consistency of the surgical approach, we excluded patients who were converted to open surgery intraoperatively, which may have had some impact on the results of the trial. Fifth, due to certain reasons, there are shortcomings in our postoperative management. We did not initiate early feeding for patients on the day of surgery, which may potentially impact the recovery of gastrointestinal function postoperatively. Finally, the specific mechanism of action of improved sleep on the recovery of gastrointestinal function is unclear, which requires more in-depth basic research.

Conclusion

In patients with pre-existing sleep disorders, improved sleep preoperatively reduced the I-FEED score on POD1 and contributed to the reduction of acute postoperative pain, the decreased need for analgesic medications, and improved patient satisfaction.

Abbreviations

Group Z	Zolpidem group
Group C	Control group
ERAS	Enhanced recovery after surgery
VAS-A	Visual analog scale for anxiety
ASA	American Society of Anesthesiologists
ECG	Electrocardiogram
SBP	Systolic blood pressure

DBP	Diastolic blood pressure
SpO_2	Pulse oximetry
IV	Intravenous
BIS	Bispectral index
POD 1	The first postoperative day
POD 3	The third postoperative day
POD 7	The seventh postoperative day
I-FEED	Intake, response to nausea treatment, emesis, exam, and duration
GABA	Gamma-amino-butyric acid
VAS	Visual analog scores
PCIA	Patient-controlled intravenous analgesia
POI	Postoperative intestinal obstruction
BMI	Body mass index
PSQI	Pittsburgh sleep quality index
LSEQ	Leeds sleep evaluation questionnaire
GTS	The ease of getting to sleep
QOS	The quality of sleep
AFS	Awakening from sleep
BFW	Behavior following wakefulness
ELISA	Enzyme-linked immunoassay
POD	Postoperative day
HPA	Hypothalamic-pituitary-adrenal
SNS	Sympathetic nervous system
NF-κB	Nuclear factor κB
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6
NO	Nitric oxide

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

Declarations

Ethics approval and consent to participate
This study was approved by The First People's Hospital of Lianyungang, Lianyungang, Jiangsu Province, China (registration number: KY-20231004002-02). Written informed consent was signed by the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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