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Effect of Remimazolam on Cellular Immune Response and Postoperative Recovery in Patients Undergoing Laparoscopic Colorectal Cancer Surgery

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ABSTRACT

We aimed to evaluate the effect of remimazolam-based general anesthesia on cellular immune function and postoperative recovery quality in patients undergoing laparoscopic radical colorectal cancer surgery.

A total of 90 patients scheduled for elective laparoscopic colorectal cancer radical surgery were randomly divided into 2 groups: the remimazolam group (Group R) and the propofol group (Group P), with 45 patients in each group. Anesthesia induction in Group R involved intravenous remimazolam, and in Group P, intravenous propofol until the loss of consciousness (modified observer's assessment of alertness/sedation [MOAA/S] score 1–2). Both groups then received intravenous sufentanil and cisatracurium for intubation. Cellular immune function markers ($CD3^+$, $CD4^+$, $CD8^+$ T and natural killer [NK] cells) were recorded at different time points. Quality of Recovery [QoR]-15 scale scores, hemodynamic parameters, sedation scores (Riker and Ramsay scales), recovery times and adverse events were also recorded.

Compared to Group P, Group R had significantly higher NK, $CD3^+$, and $CD4^+$ cell levels immediately after surgery and at 24 hours postoperatively. Group R showed a significantly lower incidence of intraoperative hypotension, bradycardia, and vasopressor use. Additionally, QoR-15 scores at 24 and 72 hours were higher in Group R. There were no significant differences in Riker or Ramsay scores, extubation time, post-anesthesia care unit stay, or the incidence of postoperative nausea, vomiting, and drowsiness between the 2 groups.

Compared with propofol, remimazolam anesthesia results in better perioperative immune function preservation, reduced intraoperative hypotension and bradycardia, and improved postoperative recovery quality in patients undergoing laparoscopic radical colorectal cancer surgery.

Keywords: Cellular immune function; Colorectal cancer surgery; General anesthesia; Natural killer cells; Postoperative recovery; Remimazolam

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INTRODUCTION

The incidence and mortality of colorectal cancer rank third and second among all types of tumors,

respectively. In recent years, the incidence and mortality rates of colorectal cancer in China have continued to increase.[1-3] Surgery remains the primary treatment for colorectal cancer patients, but both the surgical procedure and anesthesia activate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, suppressing immune function, which promotes tumor micrometastases and clinical recurrence.[4-6]

Different anesthetic agents have varying degrees of impact on the immune function of cancer patients. Among these agents, propofol exerts a lesser negative effect on immune function compared to other anesthetics and offers immune protection as well as anticancer benefits.[7] However, propofol is associated with adverse effects such as hypotension and bradycardia.

Remimazolam, on the other hand, is characterized by a high clearance rate, small steady-state distribution volume, and minimal suppression of respiratory and circulatory functions,[8] making it a promising agent for clinical use. In addition, the safety and efficacy of remimazolam for general anesthesia are non-inferior to those of propofol. Furthermore, the incidence of hypotension and hypoxemia is lower with remimazolam than with propofol.[9,10]

However, research on the effect of remimazolam on perioperative immune function in cancer patients remains limited. Therefore, this study aims to explore the effects of remimazolam on the immune function and postoperative recovery quality of patients undergoing colorectal cancer radical surgery, in order to provide a reference for the selection of anesthetics in clinical practice for such patients.

MATERIALS AND METHODS

General Information

The study involved patients scheduled for elective laparoscopic colorectal cancer radical surgery, without any restrictions on gender. Eligible participants were between 18 and 80 years of age, with a body mass index (BMI) ranging from 18.5 to 28.0 kg/m². All patients were classified as either American Society of Anesthesiologists Physical Status Classification System (ASA) grade I or II, indicating a low to moderate risk for anesthesia and surgery.

Inclusion, Exclusion, and Elimination Criteria

Participants were included only if they met specific criteria. Any patient with a known allergy to benzodiazepines or anesthetic agents was excluded, as were those with significant preoperative dysfunction of vital organs, including the respiratory, circulatory, hepatic, or renal systems. Patients showing evidence of distant metastases on preoperative evaluation, or those who had undergone chemotherapy, radiotherapy, or corticosteroid treatment prior to surgery, were not eligible for the study. Additionally, individuals with chronic use of sedatives or analgesics, those requiring perioperative blood transfusion, or participants involved in other clinical studies within the past 3 months were excluded from this trial.

Patients were also eliminated if certain intraoperative or postoperative events occurred. Specifically, if anesthesia induction or maintenance with remimazolam could not be completed, or if the surgical procedure needed to be converted from laparoscopic to open surgery due to complications, the patient would be excluded from the study. Detection of distant metastases during surgery or in postoperative pathology reports also warranted elimination. Furthermore, unplanned admission to the intensive care unit (ICU) or withdrawal from the study due to patient preference or loss to follow-up were additional grounds for elimination. Patients were randomly assigned to 1 of the 2 groups (Group R or Group P) using a computer-generated random number table. Allocation concealment was ensured using sealed, opaque envelopes, which were opened by a designated nurse not involved in the study.

Anesthesia Protocol

Before surgery, all patients were required to fast for at least 8 hours to reduce the risk of aspiration. Upon arrival in the operating room, intravenous access was established, and all essential medications were prepared. For hemodynamic monitoring, radial artery catheterization was performed under local anesthesia, and continuous monitoring of electrocardiography, invasive blood pressure, oxygen saturation (SpO_2), and bispectral index (BIS) was conducted.

During anesthesia induction, patients in Group R received intravenous remimazolam (30T06151) at a dose of 0.2 to 0.3 mg/kg over more than 1 minute, while those in Group P were administered intravenous propofol (X22084B) at a dose of 1.0 to 2.0 mg/kg. Once the patients lost consciousness, indicated by a modified observer's assessment of alertness/sedation (MOAA/S) score of 1–2, sufentanil (0.3–0.5 μg/kg) and

cisatracurium (0.15–0.2 mg/kg) were injected to facilitate endotracheal intubation.

Anesthesia maintenance involved continuous intravenous infusion. In Group R, remimazolam was infused at a rate of 1.0–2.0 $mg \cdot kg^{-1} \cdot h^{-1}$, while Group P received propofol at a rate of 4.0–12.0 $mg \cdot kg^{-1} \cdot h^{-1}$. Both groups also received remifentanil at a rate of 0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Intermittent doses of cisatracurium were administered as needed to maintain muscle relaxation throughout the surgery. The infusion rates of the anesthetic agents and remifentanil were adjusted in real time to maintain the BIS level between 40 and 60, ensuring an optimal depth of anesthesia.

Pressure-controlled ventilation was employed to maintain end-tidal carbon dioxide levels between 35 and 45 mmHg, with SpO_2 levels consistently kept above 90%. Vasopressors, such as atropine, ephedrine, or norepinephrine, were administered as necessary to maintain heart rate (HR) and blood pressure (BP) fluctuations within 20% of the baseline values. Muscle relaxants were discontinued 40 minutes prior to the end of the procedure, and all infusion pumps were stopped following skin closure to allow for smooth emergence from anesthesia. Intraoperative BP and HR were continuously monitored and maintained within 20% of the baseline values. Hypotension was defined as a mean arterial pressure (MAP) of less than 65 mmHg or a reduction in MAP exceeding 20% of the baseline. Bradycardia was defined as a heart rate of <50 beats per minute or a reduction exceeding 20% of the baseline value. Hypertension was defined as a MAP >20% above the baseline.

Postoperative Management and Blinding

After surgery, patient-controlled intravenous analgesia (PCIA) was initiated using a solution of sufentanil (0.03–0.05 $\mu g \cdot kg^{-1} \cdot h^{-1}$) diluted in saline to a total volume of 100 mL. Patients were instructed to use the analgesia pump according to standard protocols to manage postoperative pain effectively. The allocation of patients to either Group R or Group P was blinded to the participants, with anesthesiologists responsible for administering medications and managing the intraoperative course. Study personnel prepared the drugs and were tasked with data collection and postoperative follow-up.

Outcome Measures

Several outcome measures were recorded to assess the effectiveness and safety of the 2 anesthetic regimens. Hemodynamic parameters, including HR, MAP, SpO_2, and BIS, were documented at key time points: prior to anesthesia induction, immediately after intubation, at the time of skin incision, at the conclusion of surgery, and immediately following extubation. Cardiovascular adverse events were defined as fluctuations in HR or BP exceeding 20% of the baseline values, and the use of vasopressors was recorded to evaluate hemodynamic stability.

Peripheral venous blood samples were collected at 4 time points—before induction, immediately after surgery, and at 24 and 72 hours postoperatively. Immune markers were measured using flow cytometry, including CD3, CD4, CD8, and natural killer (NK) cells. CD3 serves as a marker for total T lymphocytes, indicating the overall population of T cells. CD4 marks helper T cells, which play a crucial role in releasing cytokines to support immune responses and promote antitumor activity. CD8 is associated with cytotoxic T cells, responsible for directly killing tumor cells. Lastly, NK cells represent a subset of lymphocytes that mediate non-specific, rapid cytotoxic responses against tumor and virally infected cells. The $CD4^+$:$CD8^+$ ratio was calculated to evaluate immune balance, with values between 1.2 and 2.0 indicating normal immune function. Flow cytometry analysis was performed using a multicolor panel with the following fluorochrome-labeled antibodies: CD3 (allophycocyanin; APC), CD4 (fluorescein isothiocyanate; FITC), CD8 (phycoerythrin; PE), and NK Cells (peridinin-chlorophyll protein complex conjugated with Cyanine 5.5; PerCP-Cy5.5). These fluorochromes were chosen for their compatibility with the flow cytometer used and their ability to provide clear spectral separation.

The quality of recovery was evaluated using the 15-item Quality of Recovery (QoR-15) scale, which measures the 5 domains of physiological comfort, psychological support, emotional state, physical behavior, and pain. Each domain is scored on a 0–10 scale, with a maximum total score of 150, where higher scores indicate better recovery quality.

Assessment of Recovery and Sedation

Sedation levels were measured using the Riker Sedation-Agitation Scale and the Ramsay Sedation Scale upon awakening. Recovery times were documented, including the time from the cessation of anesthetic agents to the patient opening their eyes or

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blinking spontaneously, the time from discontinuation of anesthesia to extubation, and the duration of stay in the post-anesthesia care unit (PACU). Further recovery metrics included the time to the first postoperative bowel movement, the length of postoperative hospital stay, and the incidence of nausea, vomiting, and drowsiness within the first 24 hours following surgery.

Statistical Analysis

Sample size calculations were performed using PASS 15.0 software. The primary outcome was the NK cell level at 24 hours postoperatively. Based on preliminary trial results, the NK cell level in Group P was expected to be 8.6%±3.2%, while that in Group R was expected to be 11.2%±3.5%. With an alpha value of 0.05 and a power (1−β) of 0.8, a sample size of 31 patients per group was required, assuming a 20% dropout rate. All statistical analyses were conducted using SPSS 26.0 software. Continuous variables following normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using repeated-measures analysis of variance (ANOVA) for within-group comparisons and independent *t* tests for between-group comparisons. Non-normally distributed data were presented as medians and interquartile ranges (IQRs) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as frequencies (n, %) and compared using the chi-square test or Fisher's exact test, as appropriate. A *p* value of <0.05 was considered statistically significant.

RESULTS

Patient Enrollment and Baseline Characteristics

A total of 92 patients were enrolled in the study. One patient from Group R and one from Group P were excluded due to the detection of distant metastases during surgery. No patients were lost to follow-up, resulting in 90 patients being included in the final analysis. There were no statistically significant differences between the 2 groups in terms of gender, age, BMI, ASA classification, surgical time, anesthesia duration, remifentanil dosage, or cisatracurium dosage (Table 1).

Table 1. Comparison of General and Intraoperative Characteristics Between the Two Groups

Indicator	Group R (n=45)	Group P (n=45)	*p*
Male/female (cases)	28/17	25/20	0.52
Age (years)	61.2±10.3	58.5±9.9	0.32
BMI (kg/m²)	21.8±2.9	22.1±3.3	0.41
ASA grade I/II (cases)	8/37	7/38	0.78
Surgery duration (min)	232.1±70.5	235.9±73.8	0.85
Anesthesia duration (min)	256.2±71.1	257.8±77.2	0.92
Remifentanil dosage (mg)	2.6±0.7	2.4±0.8	0.43
Cisatracurium dosage (mg)	23.5±5.8	24.3±6.7	0.67

Hemodynamic Parameters

In Group R, HR decreased significantly at the time of skin incision, and MAP dropped immediately after intubation and at skin incision compared to pre-induction values ($p<0.05$). In Group P, HR significantly decreased at the time of skin incision and immediately after surgery, while MAP significantly decreased at intubation, skin incision, and at the end of surgery compared to pre-induction values ($p<0.05$). When comparing the 2 groups, Group R showed a significantly higher HR and MAP immediately after surgery ($p<0.05$), whereas the BIS score was significantly lower in Group R immediately after extubation ($p<0.05$). No significant differences were observed in SpO_2 levels between the 2 groups at any time point (Table 2).

Table 2. Comparison of perioperative HR, MAP, SpO_2, and BIS between the 2 groups

Indicator	Time point	Group R (n=45)	Group P (n=45)	*p*
HR (bpm)	Before induction	74.9±9.7	78.2±15.4	0.21
	Immediately after intubation	71.5±11.1	75.8±12.8	0.17
	Immediately after incision	65.9±9.9 (a)	63.3±11.5 (a)	0.14
	End of surgery	76.3±14.2 (b)	67.4±12.5 (a)	0.03
	Immediately after extubation	76.5±20.6	79.1±15.0	0.52
MAP (mmHg)	Before induction	97.2±11.3	95.8±10.9	0.36
	Immediately after intubation	86.3±11.9 (a)	82.2±15.6 (a)	0.22
	Immediately after incision	87.4±10.8 (a)	88.6±13.4 (a)	0.54
	End of surgery	90.5±8.7 (b)	83.3±10.1 (a)	0.01
	Immediately after extubation	98.8±8.9	100.5±9.5	0.45
SpO_2 (%)	Before induction	95.2 (92.3–97.5)	94.8 (92.5–96.1)	0.72
	Other time points	100.0 (99.0–100.0)	99.9 (98.7–100.0)	0.87
BIS	Before induction	92.5 (91.0–96.5)	93.5 (89.5–96.8)	0.55
	Immediately after intubation	55.1 (48.2–57.9)	54.8 (48.0–59.5)	0.63
	End of surgery	54.3 (49.0–59.8)	52.2 (46.0–58.1)	0.49
	After extubation	83.0 (79.1–87.8)	85.6 (81.5–89.2)	0.39

(a) Compared with pre-induction values, $p<0.05$; (b) Compared with Group P, $p<0.05$.

Intraoperative Adverse Events

The incidence of intraoperative hypotension, bradycardia, and vasopressor use was significantly lower in Group R compared to Group P ($p<0.05$). However, no statistically significant difference was found between the 2 groups in terms of the incidence of hypertension (Table 3).

Immune Function Parameters

In Group P, NK and $CD8^+$ cells showed a significant decrease immediately after surgery, and NK cells remained significantly lower at 24 hours postoperatively compared to pre-induction levels ($p<0.05$). In contrast, no significant changes were observed in NK, $CD3^+$, $CD4^+$, or $CD8^+$ cells, or the $CD4^+$:$CD8^+$ ratio at any time point within Group R. Group R exhibited significantly higher levels of NK, $CD3^+$, and $CD4^+$ cells immediately after surgery and at 24 hours postoperatively compared to Group P ($p<0.05$). No statistically significant differences were observed between the 2 groups in NK, $CD3^+$, $CD4^+$, or $CD8^+$ cells, or the $CD4^+$:$CD8^+$ ratio before induction or at 72 hours postoperatively. Similarly, no differences were observed in $CD8^+$ cells or the $CD4^+$:$CD8^+$ ratio immediately after surgery or at 24 hours postoperatively (Figure 1).

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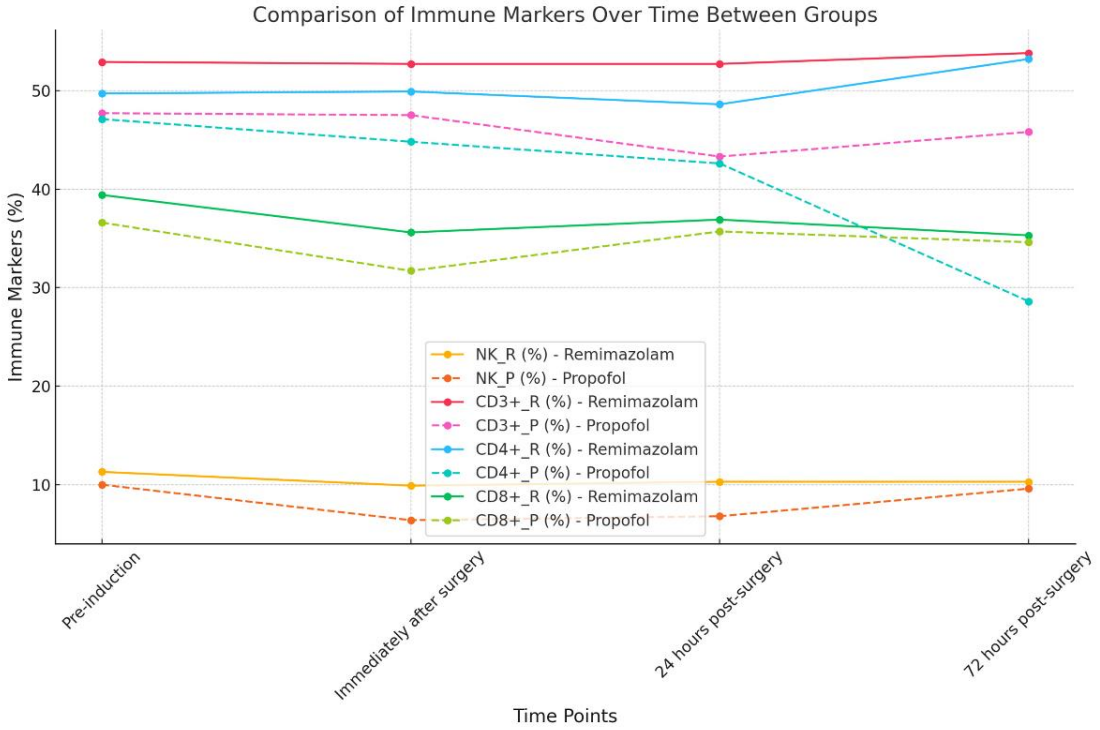

Figure 1. Comparison of immune markers over time between groups. This figure illustrates the changes in immune markers, including NK cells (%), CD3$^+$ T cells (%), CD4$^+$ T cells (%), and CD8$^+$ T cells (%), at 4 timepoints: pre-induction, immediately after surgery, 24 hours post-surgery, and 72 hours post-surgery. Data are presented separately for the Remimazolam group (Group R) and the Propofol group (Group P). NK cells (%): Natural killer (NK) cell levels were consistently higher in Group R compared to Group P at all post-surgery time points, indicating better preservation of innate immunity with remimazolam anesthesia; CD3$^+$ T cells (%): Group R demonstrated more stable CD3$^+$ T cell levels over time, suggesting less impact on overall cellular immunity; CD4$^+$ T cells (%): CD4$^+$ T cell levels remained higher in Group R immediately after surgery and at 24 hours, reflecting better maintenance of helper T cell populations; CD8$^+$ T cells (%): Both groups showed similar trends for CD8$^+$ T cells, with slightly higher levels in Group R at all time points.

Quality of Recovery (QoR-15) Scores

The QoR-15 scores at 24 and 72 hours postoperatively were significantly lower in both groups compared to pre-induction scores ($p<0.05$). However, Group R demonstrated significantly higher QoR-15 scores than Group P at both 24 and 72 hours postoperatively ($p<0.05$). Among the 5 domains of the QoR-15 scale, Group R showed significant improvements in physiological comfort, psychological support, and physical behavior at 24 hours, as well as physiological comfort and behavior at 72 hours, compared to Group P ($p<0.05$). No significant differences were found between the groups in terms of emotional state and pain at 24 hours, or in psychological support, emotional state, and pain at 72 hours (Table 4).

Sedation Scores and Recovery Metrics

There were no statistically significant differences between Group R and Group P in Riker or Ramsay sedation scores upon awakening. Similarly, no significant differences were observed between the groups in terms of recovery times, including the time to spontaneous eye-opening, extubation time, PACU stay, time to first postoperative bowel movement, and postoperative hospital stay. Additionally, the incidence of nausea, vomiting, and drowsiness within the first 24 hours postoperatively did not differ significantly between the groups (Table 5).

Table 3. Incidence of intraoperative cardiovascular events and vasopressor use

Indicator	Group R (n=45)	Group P (n=45)	*p*
Hypotension (cases, %)	5 (11.1) (a)	23 (51.1)	0<0.001
Bradycardia (cases, %)	1 (2.2) (a)	8 (17.8)	0.02
Hypertension (cases, %)	3 (6.7)	2 (4.4)	0.67
Vasopressor use (cases, %)	9 (20.0) (a)	35 (77.8)	0<0.001

(a) Compared with Group P, $p<0.05$.

Table 4. Quality of Recovery (QoR-15) scores at different time points

Indicator	Group R (n=45)	Group P (n=45)	*p*
Pre-induction	139.5 ± 3.2	138.9 ± 4.2	0.62
24 hours	95.8 ± 7.9 (a)(b)	88.1 ± 12.5 (a)	0.02
72 hours	118.1 ± 7.5 (a)(b)	110.7 ± 14.8 (a)	0.04

Table 5. Comparison of Postoperative Recovery Metrics

Indicator	Group R (n=45)	Group P (n=45)	*p*
Riker score (awakening agitation)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	1.0
Ramsay score (sedation)	2.0 (2.0–2.0)	2.0 (2.0–2.0)	1.0
Extubation time (min)	9.2±5.1	10.7±5.8	0.19
PACU stay ≤45 min / >45 min	8 / 37	12 / 33	0.45

DISCUSSION

Remimazolam was approved in China for colonoscopy in June 2020 and for anesthesia induction and maintenance in November 2021.[11] Following its market approval, numerous studies have explored the clinical application of this drug. None of the patients in this study experienced intraoperative awareness or spontaneous movement, demonstrating that both remimazolam and propofol can effectively induce and maintain anesthesia in laparoscopic radical surgery for colorectal cancer. Compared to propofol, remimazolam is associated with a lower incidence of injection pain, intraoperative hypotension, and bradycardia, resulting in better hemodynamic stability.[12-15] Intraoperative hypotension is known to increase the risk of postoperative ischemic stroke, which negatively affects patient survival rates.[16]

The results of this study showed that, compared to propofol, remimazolam caused a smaller reduction in HR and MAP during anesthesia induction. After surgery commenced, HR and BP remained stable, with significantly lower incidences of intraoperative hypotension, bradycardia, and vasopressor use in the remimazolam group. These findings suggest that remimazolam reduces cardiovascular suppression and helps maintain hemodynamic stability, which may improve patient outcomes.

Intraoperative hypotension is a critical concern, as it can compromise organ perfusion and increase the risk of postoperative complications, including ischemic events. In this study, the incidence of intraoperative hypotension was significantly lower in the remimazolam group compared to the propofol group. This may be attributed to remimazolam's minimal impact on cardiovascular function. Effective management of hypotension, including the use of vasopressors such as ephedrine or norepinephrine, likely contributed to maintaining hemodynamic stability. These findings underscore the importance of selecting anesthetics with a lower propensity for causing hypotension, particularly in patients at higher risk of cardiovascular complications.

However, this study also found that, although remimazolam anesthesia patients met the criteria for extubation, the BIS scores were significantly lower after extubation than in patients receiving propofol. Additionally, five patients in the remimazolam group exhibited drowsiness, though the difference in drowsiness between the groups was not statistically significant. This clinical observation warrants attention, as the accuracy of BIS scores in remimazolam anesthesia may be influenced by electromyographic (EMG) activity, while propofol is less affected by EMG interference.[17] Further research is needed to explore whether there is a correlation between BIS values and drowsiness following extubation in remimazolam anesthesia. Postoperative drowsiness, while generally transient, can delay recovery milestones, including early mobilization and discharge readiness. In this study, although a higher number of patients in the remimazolam group exhibited postoperative drowsiness compared to the propofol group, the difference was not statistically significant. This observation may be related to differences in pharmacodynamics or BIS scoring accuracy between the 2 agents. Further studies are warranted to explore strategies for minimizing postoperative drowsiness, such as optimizing dosage or using reversal agents like flumazenil.

The postoperative immune response is primarily related to T lymphocyte-mediated cellular immunity. $CD3^+$ cells reflect overall cellular immune function, while $CD4^+$ cells, which act as helper T cells, release cytokines to enhance antitumor activity upon activation.[18] $CD8^+$ cells are cytotoxic T cells that kill tumor cells and may influence antitumor responses and patient outcomes.[19-21] A $CD4^+$:$CD8^+$ ratio between 1.2 and 2.0 is a critical marker of immune system stability. NK cells, as part of the innate immune system, provide rapid, nonspecific immune responses against potential threats, including viruses and cancerous cells.[22-24]

NK cells are critical components of the innate immune system, capable of identifying and eliminating tumor cells without prior sensitization. Their activity is a marker of immune competence and has been shown to correlate with better cancer outcomes. The observed higher levels of NK cells in the remimazolam group suggest that this anesthetic may help preserve innate immunity during the perioperative period, potentially reducing the risk of tumor recurrence. $CD3^+$ T cells represent the overall population of T lymphocytes, playing a central role in adaptive immunity. $CD4^+$ helper T cells are pivotal in orchestrating immune responses and enhancing antitumor activity through cytokine release. Conversely, $CD8^+$ cytotoxic T cells directly kill tumor cells. Maintaining a stable $CD4^+$:$CD8^+$ ratio, as observed in the remimazolam group, is crucial for balanced immune regulation. The preservation of $CD3^+$ and $CD4^+$ T cell levels in the remimazolam group suggests that this agent may support adaptive immunity during surgery, potentially improving long-term cancer control.

Surgery, as a primary treatment for tumors, induces stress responses that suppress immune function, characterized by reduced numbers and activity of T lymphocytes (including $CD4^+$, $CD8^+$, and $CD3^+$ cells), impaired NK cell function, and increased lymphocyte-to-neutrophil ratios. These changes may promote tumor recurrence and metastasis.[25] Therefore, it is essential to select anesthetics that minimally affect perioperative immune function in cancer patients.

Propofol has shown anticancer effects through various mechanisms.[26,27] However, previous studies have indicated that, compared to propofol, remimazolam better preserves immune function in breast cancer patients, with higher postoperative levels of NK, $CD3^+$, and $CD4^+$ cells, as well as an increased $CD4^+$:$CD8^+$ ratio.[9,28] In this study, the decrease in NK, $CD3^+$, and $CD4^+$ cells immediately after surgery and at 24 hours postoperatively was less pronounced in the remimazolam group than in the propofol group. Furthermore, in contrast to propofol, remimazolam did not cause significant changes in NK, $CD3^+$, $CD4^+$, or $CD8^+$ cell levels or the $CD4^+$:$CD8^+$ ratio at any monitoring time point. These findings suggest that remimazolam exerts a smaller impact on immune function during surgery, thereby helping maintain

perioperative immune stability and potentially improving patient prognosis.

The QoR-15 scale is an effective, reliable, and sensitive patient-centered tool for assessing postoperative recovery, with significant clinical utility.[29,30] Although laparoscopic colorectal cancer surgery is less invasive and has fewer postoperative complications than open surgery, factors such as postoperative placement of nasogastric and urinary catheters and colostomy procedures may affect patients' emotional states and recovery.[31,32]

In this study, both remimazolam and propofol were associated with significant reductions in QoR-15 scores at 24 and 72 hours postoperatively. However, the remimazolam group showed significantly higher QoR-15 scores than the propofol group at both time points. Specifically, patients in the remimazolam group reported higher scores in physiological comfort, psychological support, and behavior at 24 hours, as well as in physiological comfort and behavior at 72 hours. These findings suggest that remimazolam may improve postoperative recovery quality by reducing respiratory depression, enhancing sleep quality, and improving emotional well-being.

Previous evidence reported that the use of remimazolam improved postoperative recovery quality, possibly by reducing the incidence of nausea and vomiting.[33] However, nausea and vomiting are also known adverse effects of remimazolam. In this study, fewer patients in the remimazolam group experienced nausea and vomiting compared to the propofol group, although the difference was not statistically significant within the first 24 hours postoperatively. Further clinical studies are needed to explore whether remimazolam can reduce postoperative nausea and vomiting and improve recovery quality compared to propofol.

Remimazolam, as an ultra-short-acting drug, does not accumulate even with prolonged infusion. It is metabolized by tissue esterases into an inactive metabolite, carboxylic acid, and is rapidly eliminated after drug discontinuation. However, there is ongoing debate regarding whether remimazolam or propofol provides faster recovery and extubation times. Phase III clinical trials conducted in Japan and China have reported that remimazolam anesthesia resulted in longer recovery and extubation times than propofol. Conversely, Previous evidence[12] found that remimazolam led to shorter recovery and extubation times than propofol. Similarly, Tang et al[34] reported higher awakening quality (as indicated by Ramsay sedation scores) with remimazolam, although the difference in recovery times was not statistically significant.

In this study, no significant differences were observed between the 2 groups in recovery time, extubation time, or length of postoperative hospital stay. Additionally, there were no statistically significant differences in Riker and Ramsay sedation scores between the two groups upon awakening. These results suggest that remimazolam does not significantly improve awakening quality compared to propofol, but further studies are needed to explore other factors influencing awakening quality.

This study has several limitations. Other stress markers, such as blood glucose, lactate, and catecholamines, were not evaluated. The parameters and time points used to assess awakening quality were relatively limited. Additionally, the short follow-up period only allowed for the assessment of immune function and QoR-15 scores up to 72 hours postoperatively. Future retrospective studies are needed to analyze the long-term impact of remimazolam on patient outcomes.

The management of these adverse events not only influences immediate intraoperative and postoperative safety but also impacts longer-term outcomes, such as patient satisfaction, recovery quality, and risk of complications. The findings from this study suggest that remimazolam may offer advantages in mitigating intraoperative hypotension without significantly increasing other adverse events, such as postoperative drowsiness. These benefits could contribute to better overall recovery and prognosis in colorectal cancer surgery patients.

In conclusion, compared with propofol, remimazolam-based general anesthesia exerts a smaller impact on cellular immune function in patients undergoing colorectal cancer surgery. It is also associated with a lower incidence of intraoperative hypotension and bradycardia and improved postoperative recovery quality.

STATEMENT OF ETHICS

This study received approval from the Ethics Committee of the Affiliated Hospital of Shandong Second Medical University (Approval No. 22-SSMU-547; clinical trial code: ChiCTR2300070998). Informed

consent was obtained from all participants or their legal guardians prior to enrollment.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

Upon reasonable request from the corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

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