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CLINICAL TRIAL REPORT

Effect of Remimazolam- Vs Propofol-Based Intravenous Anesthesia on Surgical Stress Response and Post-Operative Immune Function in Patients with Gastric Radical Surgery

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Purpose: This study aimed to compare the impact of remimazolam-based versus propofol-based intravenous anesthesia on surgical stress and post-operative immune function in patients undergoing gastric radical surgery.

Patients and Methods: Sixty-eight patients aged 50 to 80 undergoing gastric radical surgery were randomly assigned to the remimazolam group (group R) or the propofol group (group P), receiving remimazolam or propofol-based intravenous anesthesia, respectively. The primary outcome measured was peri-operative serum stress indicators and lymphocyte subtypes. Secondary outcomes included hemodynamic vitals, recovery quality, postoperative pain profiles and potential adverse effects.

Results: The demographic and surgical characteristics of the 60 analyzed patients were comparable. The absolute counts of CD3+CD4+ and CD3+CD8+ cell decreased significantly on POD1 compared with baseline. On POD3, the numbers of CD3+CD4+ cells in group R were lower than baseline and Group P, whereas the CD3+CD8+ cell counts in both groups were lower than baseline, with group R higher than group P. The CD3-CD16+CD56+ cell numbers in both groups on POD1 and POD3 decreased significantly compared to baseline with group P lower than group R on POD3. The serum levels of IL-1β, IL-6, TNF-α, ACTH and COR rose sharply 2 hours after the beginning of surgery compared to baseline. Notably, all these parameters in group R were higher than those in group P. Additionally, blood pressure and intra-operative vasoactive drug frequency in group R were higher than that in group P. No significant differences in recovery quality, postoperative pain profiles, and potential adverse effects were observed.

Conclusion: Remimazolam-based intravenous anesthesia might favour the recovery of cellular immune function in early post-operative period compared to propofol. On the contrary, remimazolam was inferior to propofol in suppressing surgical stress. Further studies with larger sample sizes are needed to confirm our findings.

Keywords: remimazolam, propofol, surgical stress, post-operative immune function, gastric radical surgery

Introduction

Remimazolam is a novel water-soluble, ultra-short-acting benzodiazepine (BDZ). Similar to other BDZs, remimazolam enhances γ-amino-butyric acid A (GABAA) receptor activity and increases chloride ion flux, causing membrane hyperpolarization and inhibition of neuronal activity, thereby inducing anxiolysis, amnesia, and sedation.[1] Owing to its structural soft drug design, analogous to remifentanil, incorporating a carboxylic ester moiety into the BDZ core,[1] remimazolam can be rapidly hydrolyzed to a pharmacologically inactive metabolite (CNS 7054) via non-specific tissue esterase activity. This results in its favorable pharmacological properties, including rapid onset, organ-independent metabolism, short duration of action, predictable recovery, and the availability of a reversal agent.[2,3]

Despite the initial market positioning of remimazolam for outpatient non-intubation procedure sedation,[4] such as endoscopic operations, its application scope quickly expanded to include the induction and maintenance of general

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anesthesia as research progressed. Previous publications largely focused on the application of remimazolam in various clinical contexts, demonstrating its efficacy and safety in procedure sedation and general anesthesia[5–8].

The immunosuppressive response triggered by surgical trauma is widely regarded as a key determinant of post-operative complications, such as end-organ damage, infections, and protracted recovery.[9] Furthermore, some clinical studies suggested that postoperative immunosuppression be associated cancer recurrence and metastasis.[10] The effects of anesthetic agents on immune function have garnered increasing interest and attention in recent years. However, there are a few reports about the impact of remimazolam on surgical stress response and post-operative immune function. Therefore, the primary objective of this study was to investigate the effects of remimazolam-based intravenous anesthesia on stress response and post-operative immune function compared with propofol in patients undergoing gastric radical surgery.

Ethical Considerations

This prospective, randomized, controlled, single-blind study was approved by the Ethics Committee of Affiliated Yixing Hospital of Jiangsu University (approval number: LS2021K045) and conducted in accordance with the principles of the Helsinki Declaration on Human Experimentation. This trial was registered at the Chinese Clinical Trial Registry (ChiCTR2100047957), accessible at https://www.chictr.org.cn/showproj.html?proj=128098. All participants provided written informed consent.

Inclusions and Exclusions

From July 2021 to December 2021, patients aged 50 to 80 years with gastric cancer, verified by endoscopy, biopsy, and preoperative enhanced computed tomography scans of the abdominal pelvis indicating cT1-2N0M0 (determined using Japanese Gastric Cancer Association classifications), were eligible for inclusion in this study. Exclusion criteria were as follows: 1) allergy to remimazolam; 2) pre-operative severe organ function impairment or American Society of Anesthesiologists grade III and above; 3) history of immune system disorders; 4) pre- and intra-operative chemotherapy or radiotherapy; 5) recent exposure to immunosuppressants or other BDZs; 6) postoperative serious complications; 7) re-operation during hospitalization.

Randomizations and Masking

Patients were randomly assigned to either the remimazolam(R) or propofol(P) groups in a 1:1 ratio using a computer-generated random sequence and sealed envelope method by a medical statistician (Wang Chunhui). The attending anesthesiologist, who was not blinded to the group assignments due to the significantly different properties of the two anesthetics, was responsible for anesthesia management but was not permitted to participate in the statistical analysis. Patients, surgeons, and study investigators were blinded to group identity. The investigators assessing study outcomes and the patients were blinded to group allocation throughout the study period.

Anesthesia and Perioperative Care

No premedication was administered to any of the patients. All patients received standard monitoring, which included pulse oximetry, invasive monitor of arterial blood pressure, electrocardiography, bispectral index (BIS) monitor, and carbon dioxide capnography.

For the R group, induction was conducted with continuous infusion of remimazolam at a rate of 6 mg kg^{-1} h^{-1} until loss of consciousness followed by sufentanil (0.3 μg/kg) and cisatracurium (0.15 mg/kg). Following intubation, remimazolam 1–2 mg kg^{-1} h^{-1} combined with remifentanil 15–40 μg $kg^{-1}h^{-1}$ was titrated to maintain hemodynamic stability and adequate depth of anesthesia (BIS values 40–60). Intermittent injections of cisatracurium were administered to maintain muscle relaxation. In Group P, propofol (1.5 mg/kg), sufentanil (0.3 μg/kg) and cisatracurium (0.15 mg/kg) were sequentially intravenous infused for induction and propofol 1–2 mg kg^{-1} $h^{-1,}$ remifentanil 15–40 μg $kg^{-1}h^{-1}$, and intermittent cisatracurium for maintenance. All patients received mechanically ventilated with 60% oxygen, tidal volume (TV) 8–10mL/kg, frequency 10–14/min, keeping an end-tidal CO2 of 30–40 mmHg during the surgery procedure. Sufentanil 0.2μg/kg was administered before the skin incision and ketorolac 30mg 5 minutes before sewing. All

anesthetics were discontinued at the completion of surgery. Extubation was performed after consciousness recovery and spontaneous respiration. Flumazenil, the specific benzodiazepine antagonist, was not administered during the recovery stage. Patient-controlled intravenous analgesia (PCIA), consisting of 100 μg sufentanil in 100 mL normal saline, was administered by an AutoMed 3200 pump at a background rate of 2 mL/h and a bolus dose of 2 mL with a lockout interval of 15 minutes. Rescue analgesia was provided with ketorolac (30 mg) intramuscularly injection whenever the patient complained of a Visual Analogue Scale (VAS) score equal to or more than 4, and the maximum total daily was not allowed exceed 120mg.

Outcomes

The primary outcome was the peri-operative serum stress indicators (cortisol COR, adrenocorticotropic hormone ACTH, interleukin-1 IL-1β, interleukin-6 IL-6, tumor necrosis factor-α TNF-α) and lymphocyte subtypes (CD3+CD4+, CD3+CD8+, CD3-CD19+, CD3+CD4+/CD3+CD8+, CD3-CD16+CD56+ cell). Venous blood samples (10 mL) were collected at baseline (T0), 2h after beginning of the operation (T4), postoperative day (POD) 1 (T6), POD 3 (T7). Blood lymphocyte subsets were analyzed using flow cytometry at T0, T6, and T7 with a NovoCyte D3000. Serum levels of IL-1β, IL-6, and TNF-α at T0, T4, and T6 were measured using a commercial ELISA kit (NeoBioscience, US, EHC002bQT.96, EHC007QT.96, EHC103AQt.96). ACTH and COR levels at T0, T4, and T6 were determined using the chemiluminescence method. Secondary outcomes included peri-operative hemodynamic vitals (baseline T0, after induction T1, immediately after intubation T2, 5 min after beginning of the operation T3, 2 hours after beginning of the operation T4, 5 min after extubation T5), recovery quality (consciousness recovery time, extubation time, PACU stay, delayed emergence, and SPO2<93% 10 minutes after extubation), postoperative pain profiles (VAS score POD1, POD2, number of the pump press, and rescue analgesia) and potential adverse effects (injection pain, and post-operative nausea and vomiting PONV).

Sample Size Calculation

The sample size was calculated using PASS 15.0 software. A pilot study was conducted to assess the difference between baseline blood glucose levels and those measured 2 hours after the commencement of surgery as an index of stress response. The observed difference between the remimazolam (R) and propofol (P) groups was 0.9 mmol/L, with an estimated standard deviation of 1.2 mmol/L. According to the significance level of 0.05 and the power of 0.8, the required sample size was 29 individuals for each group. An additional 15% was included to account for potential missing data and attrition, resulting in a final sample size of 68 patients (34 patients per group).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM SPSS, Armonk, NY). Continuous variables were presented as a mean or median (interquartile range) and processed with Student's *t*-test or the Wilcoxon rank-sum test, as appropriate, according to normality distribution. Categorical variables were presented as the number of patients and processed with the Chi-squared test or Fisher's exact probability test. Data with repeated measures were analyzed using repeated-measures ANOVA. Statistical significance was set at $P < 0.05$.

Results

A flow diagram of the study is illustrated in Figure 1. A total of 68 patients were scheduled to undergo gastrointestinal surgery under TIVA were recruited for this study. Eight patients were excluded due to intraoperative intra-peritoneal chemotherapy (5), postoperative serious complications (2), and re-operation (1). Ultimately, 60 patients were included in the analysis, 30 in each group.

No significant difference was observed between the two groups in terms of demographic and clinical data including age, sex, body mass index (BMI), smoking, alcohol, comorbidities (hypertension, diabetes mellitus DM), duration of operation and anesthesia, intra-operative remifentanil and sufentanil consumption, blood loss, urine output, fluid infusion, blood transfusion, postoperative hospital stay (P>0.05), except for the intra-operative vasoactive drug frequency in R group higher than in P group (P < 0.05) (Table 1).

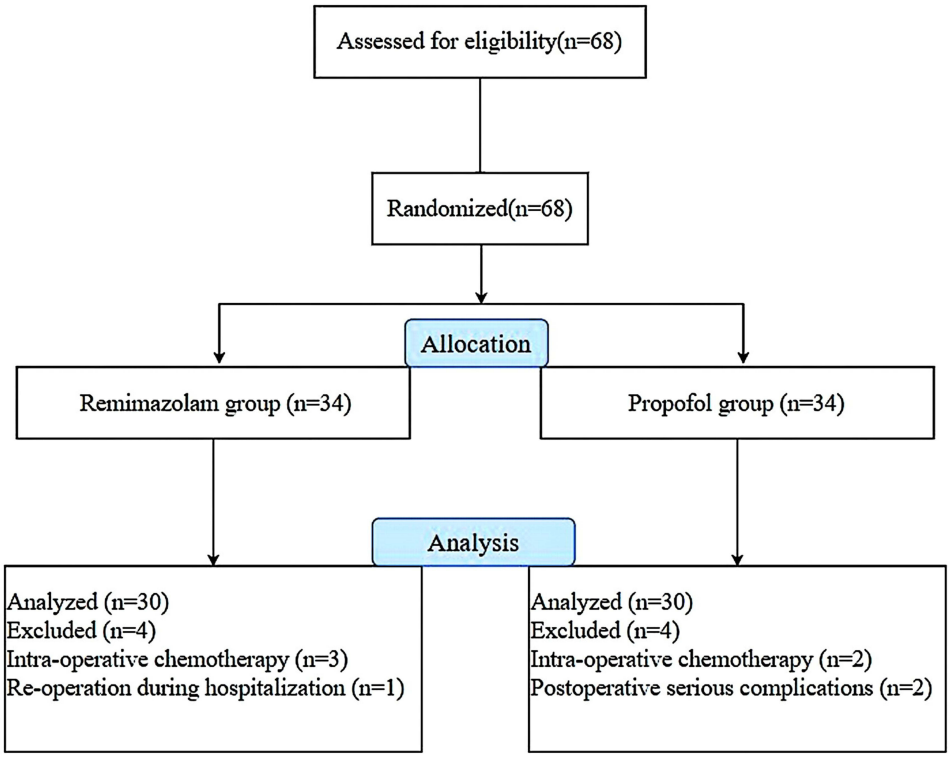

Figure 1 Enrollment flowchart.

The perioperative hemodynamic variables are shown in Figure 2. No significant differences were observed in heart rate between the groups at any time point. Nevertheless, the mean arterial pressure in group R was higher than that in group P on T1, T2, T3, and T5.

Table 2 illustrates the lymphocyte subtypes at various time points. Although the ratios of CD3+CD4+ and CD3+CD8+ cells remained unchanged throughout the perioperative period, the absolute counts of CD3+CD4+ and CD3+CD8+ cells decreased significantly on POD1 compared to baseline. Moreover, the absolute counts of $CD3^{+}CD4^{+}$ cells in

Table 1 Demographic, Clinical, and Surgical Characteristics

	Group P (n=30)	Group R (n=30)	*P* value
Age(year)	68.2±7.5	66.8±8.3	0.341
Gender(M/F)	23(76.7%)/7(23.3%)	22(73.3%)/8(26.7%)	0.766
BMI(kg/m^2)	23.8±1.3	24.0±1.5	0.635
Hypertension(%)	7(23.3%)	5(16.7%)	0.518
Diabetes mellitus(%)	4(13.3%)	3(10%)	0.687
Duration of anesthesia(min)	153.6±21.1	148.4±19.5	0.892
Duration of operation(min)	132.4±12.6	129.2±11.3	0.335
Sufentanil consumption(ug)	42.6±5.9	46.1±7.1	0.051
Remifentanil consumption(ug)	663.4±30.6	692.5±44.3	0.208
Vasoactive agents use(%)	2(6.7%)	9(30%)	0.041
Blood loss(mL)	87.7±14.4	103.2±23.6	0.741
Fluid infusion(mL)	1170.3±121.8	1241.7±146.4	0.573
Blood transfusion(%)	4(13.3%)	5(16.7%)	0.765
Urine output(mL)	252.6±29.5	284.1±24.1	0.873
Postoperative hospital stay(day)	11.5±2.3	12.2±1.7	0.457

Notes: Data are presented as mean (SD) or n (%).
Abbreviations: M, male; F, female; BMI, body mass index, R, remimazolam; P, propofol.

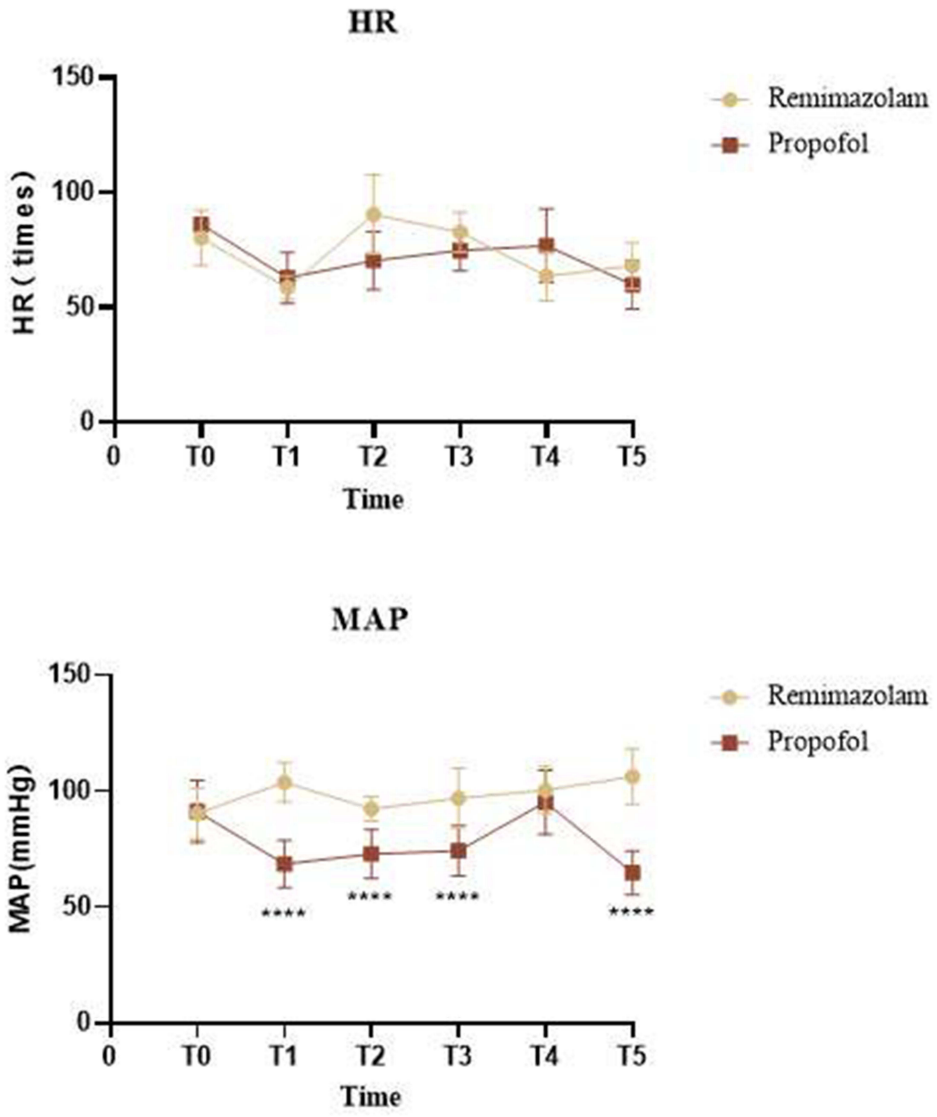

Figure 2 Peri-operative hemodynamic variables, encompassing HR and MAP. Significant reduction in MAP was observed at T1, T2, T3, T5 in Propofol group compared to Remimazolam group.
Notes: T0: baseline, T1: after induction, T2: immediately after intubation, T3: 5 min after beginning of the operation, T4: 2h after beginning of the operation, T5: 5 min after extubation.
Abbreviations: HR, heart rate; MAP, mean blood pressure.

R group on POD3 were lower than baseline and Group P. Similarly, the $CD3^{+}CD8^{+}$ cell counts in both groups at POD3 were less than baseline with group R higher than group P. As to $CD3^{-}CD19^{+}$ cells, despite no change in cell number at POD1, the proportion increased. Interestingly, the $CD3^{-}CD19^{+}$ cell counts at POD3 were lower than baseline. The ratio of $CD3^{+}CD4^{+}$cell/$CD3^{+}CD8^{+}$ cell alter slightly peri-operatively, except for group P on POD3 higher than baseline. With respect to $CD3^{-}CD16^{+}CD56^{+}$ cells, the counts in both groups on POD1 and POD3 decreased significantly compared to baseline with group P lower than group R on POD3.

Table 3 presents the alterations in cytokines and stress hormones throughout the surgical procedure. Serum levels of IL-1β, IL-6, TNF-α, ACTH and COR rose sharply 2 hours after the beginning of surgery compared to baseline. Notably, all of these parameters in group R were higher than those in group P. The cytokine levels on POD1 remained higher than before surgery except for TNF-α in group P, and inter group differences still existed. The concentrations of ACTH and COR in group R on POD1 were markedly higher than the preoperative values. Conversely, the COR level in group P was

Table 2 Comparison of Lymphocyte Subtypes in Two Groups

Parameter	Group	T_0	T_6	T_7
$CD3^+CD4^+$(%)	P	34.0±6.7	34.6±6.9	39.2±6.0
	R	35.5±6.8	32.6±7.0	38.0±6.1
$CD3^+CD4^+$(n)	P	483.5±98.6	297.3±92.2[a]	494.7±101.3
	R	471.7±97.4	243.9±91.8[a]	302.5±98.4[ab]
$CD3^+CD8^+$(%)	P	25.8±4.5	21.7±3.8	25.2±4.0
	R	23.3±4.7	24.9±4.0	22.6±4.2
$CD3^+CD8^+$(n)	P	380.6±78.5	183.2±84.2[a]	192.5±80.4[a]
	R	358.6±77.0	198.5±86.5[a]	252.9±81.4[ab]
$CD3^-CD19^+$ (%)	P	9.1±2.1	15.7±2.3[a]	12.1±2.2
	R	9.5±2.0	13.9±2.4[a]	11.9±2.1
$CD3^-CD19^+$(n)	P	134.7±21.2	140.0±24.4	88.4±18.2[a]
	R	125.5±23.4	108.5±21.6	108.7±19.5
$CD4^+/CD8^+$	P	1.6±0.2	1.8±0.3	2.0±0.4[a]
	R	1.7±0.3	1.6±0.2	1.9±0.3
$CD3^-CD16^+CD56^+$ (%)	P	27.1±5.4	24.0±5.3	20.4±4.9[a]
	R	28.5±5.3	24.1±5.2	23.7±5.0[ab]
CD3-$CD16^+CD56^+$(n)	P	382.7±75.6	184.8±64.4[a]	144.9±53.6[a]
	R	408.5±70.4	183.1±65.7[a]	186.7±54.5[ab]

Notes: Compared with T0, a $P<0.05$; Compared with group P, b $P<0.05$.T0: baseline, T6: postoperative day 1, T7: postoperative day 3.
Abbreviations: R, remimazolam; P, propofol.

Table 3 Comparison of Stress and Inflammation Indicators

	Group	T_0	T_4	T_6
IL-6	R	1.7±0.2	26.6±2.7[ab]	94.7±8.9[ab]
	P	1.5±0.1	19.1±2.9[a]	75.2±8.7[a]
IL-1β	R	2.1±0.4	3.8±0.3[ab]	5.4±0.4[ab]
	P	1.7±0.3	2.2±0.2[a]	3.2±0.3[a]
TNF-α	R	19.5±3.6	31.4±3.9[ab]	24. 2±3.7[b]
	P	16.3±3.5	24.9±3.8[a]	19.1±3.6
ACTH	R	45.5±9.8	414.8±81.3[ab]	39.8±7.6[b]
	P	42.6±10.3	266.1±74.6[a]	12.3±4.5[a]
COR	R	14.6±4.7	30.9±8.2[a]	24.4±10.1[ab]
	P	15.5±4.1	28.2±8.3[a]	16.8±5.2

Notes: Compared with T0, a $P<0.05$; Compared with group P, b $P<0.05$.
T0: baseline, T4: 2h after beginning of the operation, T6: postoperative day 1.
Abbreviations: IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, tumor necrosis factor-α; ACTH, adrenocorticotropic hormone; COR, cortisol; R, remimazolam; P, propofol.

equivalent to preoperative level. Furthermore, the ACTH concentration in group P was significantly lower than the preoperative level.

Table 4 provides a summary of the patients' recovery quality. No significant differences were observed between the two groups regarding consciousness recovery time, extubation time, PACU stay, delayed emergence, and SpO2 <93% 10 minutes post-extubation. None of re-sedation patient was observed following the operation.

The two groups' pain profiles, including VAS score POD1, POD2, number of the pump press, and rescue analgesia, did not differ significantly (Table 5). Regarding adverse reactions, the incidence of injection pain in group P was higher than that of group R, while the frequency of PONV was comparable (Table 6).

Table 4 Comparison of the Recovery Quality in the Two Groups

	Group P	Group R	*P* value
Consciousness recovery time(min)	13.5±4.4	14.6±5.3	0.141
Extubation time(min)	24.8±12.3	26.4±10.4	0.638
PACU stay(min)	45.7±8.2	53.3±8.8	0.896
Delayed emergence (%)	4(13.3%)	2(6.7%)	0.389
SPO_2<93% 10 minutes after extubation (%)	1(3.3%)	1(3.3%)	0.999
Re-sedation(%)	0	0	

Notes: Values are mean±SD or number (%).
Abbreviations: PACU, Post-Anesthesia Care Unit; SPO_2, Blood Oxygen Saturation; R, remimazolam; P, propofol.

Table 5 Comparison of Postoperative Pain Profiles in the Two Groups

	Group P	Group R	*P* value
VAS score POD1	1.6±0.8	1.8±0.9	0.093
VAS score POD2	1.1±0.5	1.2±0.5	0.341
Number of the pump press	2.6±0.8	2.8±1.1	0.794
Rescue analgesia (%)	3(10%)	2(6.7%)	0.640

Notes: Values are mean±SD or number (%).
Abbreviations: VAS, Visual Analogue Scale; POD, Post-Operative Day; R, remimazolam; P, propofol.

Table 6 Comparison of the Adverse Reactions in the Two Groups

	Group P	Group R	*P* value
Injection pain	6(20%)	1(3.3%)	0.044
PONV	4 (13.3%)	3 (10%)	0.687

Notes: Values are number (%).
Abbreviations: PONV, Post-Operative Nausea and Vomiting; R, remimazolam; P, propofol.

Discussion

As an ultra-short-acting general anesthetic, remimazolam's comparison with propofol is of significant interest. Previous studies mainly focused on safety and efficacy of remimazolam and revealed similar or even superior properties compared to propofol, suggesting its potential as a viable alternative. It is well established that the perioperative period is characterized by significant alterations in host immunity, which can lead to adverse outcomes such as infections, cancer recurrence, and organ failure.[11] Large clinical studies have demonstrated that the choice of anesthetic technique may have an impact on postoperative outcomes through differential immune modulation.[12] Therefore, paying enough attention to the effect of remimazolam on postoperative immune function is of clinical significance.

Our trial demonstrated a greater restoration of CD3+CD8+ cells in group R on POD3, indicating that remimazolam may offer superior postoperative immune protection compared to propofol. However, on the other, remimazolam exhibited inferior surgical stress suppression, which demonstrated by higher stress indicators and cytokine level and hemodynamic instability.

Surgical operation causes a variety of immunological disturbances depend on the degree of surgical trauma, manifested circulating numbers of all lymphocyte subpopulations fell significantly following surgery except for B lymphocytes, which return to pre-operative values by POD 7.[13] Our study revealed that the numbers of both CD3+CD4+ and CD3+CD8+ cells decreased in both groups on POD 1 and POD 3, with a trend towards restoration of

T lymphocytes by POD 3, thereby confirming alterations in the immune system in response to surgical stress. Moreover, we observed a notable difference in T lymphocyte counts on POD3. The $CD3^+CD8^+$ T cells, also known as killer T cells, which carry out the immune response mainly by recognizing and killing target cells of infectious pathogens and are one of the key components of the cell-mediated immune response,[14] was higher in group R than that in group P, implying remimazolam superior to propofol in postoperative immune function recovery. Another lymphocyte subtype, CD3-CD16+CD56+ cells, well known by NK cells, are innate cytotoxic lymphocytes with adaptive immune characteristics,[15] which destroy pathogen-infected and tumor cells by releasing cytotoxic granules containing perforin and granzymes to initiate an apoptotic signaling cascade in target cells. NK cells play a crucial role in anti-tumour immunity because of their innate ability to differentiate between malignant versus normal cells.[15,16] We also found the higher counts and proportion on POD 3 in group R, supporting the viewpoint mentioned above that remimazolam might promote early postoperative cellular immune function compared to propofol. However, our findings contrast with those of a recent study by Qi Xing and et al[17] who reported no significant differences in CD3+CD4+ cells, CD3+CD8+ cells, and NK cells between the remimazolam and propofol groups during the perioperative period. The diversity of surgical types and calculating only the proportion of T lymphocyte subtype but not the counts may contribute to the varied conclusions.

Beyond its immunological effects, the surgical stress response involves neuroendocrine dysregulation and cytokine production, marked by elevated secretion of pituitary hormones and activation of the sympathetic nervous system.[18] This response is considered an innate survival mechanism aimed at rapidly restoring homeostasis following injury. However, an inadequate, exaggerated, or pro-longed stress response plays a major role in organ injury and dysfunction, which is the pathophysiological basis of postoperative major adverse events, acute illness and outcome.[19] Moderating the surgical stress response to minimize the negative effects produced has been the principle of enhanced recovery after surgery (ERAS).[20,21] Our study showed that all the stress indicators and cytokines of both groups increased 2 hours after beginning of procedure, and the secretion of COR, ACTH and TNF-α declined on POD 1 in contrast to the levels of IL-6 and IL-1β continuously increased. These findings were consistent with the physiological response to surgical trauma.[22] Notably, significant differences were observed between the two groups in all parameters at intra- and postoperative time points. Our results suggest that propofol may be more effective than remimazolam in controlling surgical stress. This is supported by evidence showing that the remimazolam group required more vasoactive drugs and exhibited elevated blood pressure compared to the propofol group. However, the data is contrary to Zhang' study,[23] in which the cortisol level significantly lower in the remimazolam group concluded that remimazolam relieve stress response better than propofol. Variations in surgical types, measurement time points, and the use of adjunctive nerve block technology may partly account for these discrepancies.

The recovery quality associated with remimazolam-based intravenous anesthesia has been a prominent research focus in the past three years. Numerous studies comparing the recovery effects of remimazolam with propofol have produced a range of seemingly contradictory conclusions.[8,24–26] These discrepancies may be attributed to variations in surgical procedures, differences in recovery assessment systems, and the presence of flumazenil. In the present study, we evaluated the recovery quality from two dimensions: consciousness recovery and respiratory depression after extubation, and no remarkable inter-group difference was found. Our findings suggest that remimazolam and propofol have similar effects on recovery quality, aligning with the conclusions of Choi JY's study.[8]

The comparison of remimazolam versus propofol-based intravenous anesthesia with respect to postoperative analgesia has yielded inconsistent results.[8,27] Our analysis did not reveal significant differences in VAS pain scores or analgesic drug consumption, reinforcing the notion that remimazolam lacks inherent analgesic properties.[2] The lower incidence of injection pain of remimazolam compared to propofol has been widely reported[5,28,29] and was proved in this study. Moreover, our study reached the consistent conclusion with previous studies[8,30,31] that remimazolam and propofol have similar effect regarded PONV. Furthermore, with respect to the serious adverse event,[32] we did not observe the occurrence of re-sedation due to our restriction of flumazenil. Even so, re-sedation remains an issue of concern.

Nonetheless, our study has several limitations. First, although we detected the number and proportion of lymphocyte subtypes in peripheral blood, the lack of further testing of their cellular function limited our understanding of immune function. Second, cortisol measurement in our study was immunoassays but not the standard technique,[33] liquid chromatography/tandem mass spectrometry (LC/MS), which might not detect the free cortisol level. Third, the

comparison of the consciousness recovery time between the two groups may not be accurate due to our restriction of flumazenil. Furthermore, pain is an important factor affecting stress hormone levels and immune function. Although both groups of patients had homogenized perioperative pain management strategy and comparable postoperative NRS scores, individual differences in pain were inevitable. Finally, we used use BIS to adjust anesthesia depth. In spite of an acceptable correlation with the effect-site remimazolam concentration and BIS,[34] previous studies showed that BIS values were significantly higher in the remimazolam group than in the propofol in the same sedation level assessed by Modified Observer's Assessment of Alertness and Sedation (MOAA/S).[35] This means the possibility of excessive sedation in our study.

Conclusion

In conclusion, remimazolam-based intravenous anesthesia may promote improved recovery of cellular immune function during the early postoperative period compared with propofol. Despite comparable recovery quality, postoperative pain profiles, and adverse effects, hemodynamics instability and weaker inhibitory to surgical stress could offset the immunological superiority. Further investigation is necessary to identify the potential differences in neuroendocrine and immune changes triggered by surgical trauma between remimazolam and propofol.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, search literature, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting and writing, revised the article, reviewed and agreed on all versions of the article before the article has been submitted, final version accepted for publication, and any significant changes introduced at the proofing stage, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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