CLINICAL TRIAL REPORT

Comparison of Remimazolam Tosilate and Propofol Sedation on the Early Postoperative Quality of Recovery in Patients Undergoing Day Surgery: A Prospective Randomized Controlled Trial

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Purpose: Remimazolam tosilate is a novel ultrafast-acting benzodiazepine that has a rapid emergence even after continuous infusion when using flumazenil. So far, relatively few articles are still focusing on the quality of recovery after general anesthesia with remimazolam, especially in day surgery. This study aimed to compare the early postoperative quality of recovery of remimazolam tosilate with flumazenil and propofol in patients undergoing day surgery.

Patients and Methods: 137 patients scheduled for day surgery were randomly divided into the remimazolam tosilate or propofol group. The primary endpoint was the incidence of overall recovery assessed with the early postoperative quality of recovery scale (PostopQRS) on postoperative day 1 (POD 1). The Richmond Agitation-Sedation Scale (RASS) scores in the post-anesthesia care unit (PACU), extubation time, postoperative recovery profiles, and perioperative data were documented. Any adverse events were recorded.

Results: The incidence of overall recovery on POD1 was 47.7% in the remimazolam tosilate group and 65.1% in the propofol group (odds ratio, 0.52; 95% confidence interval (CI) 0.26 to 1.06; $P = 0.072$). In general, the overall recovery of the PostopQRS increased over time, and its interaction between time and group was significant ($P = 0.003$). Among the five dimensions of PostopQRS, there exist statistical differences between groups including emotional state and cognitive recovery. Upon arrival at the PACU, the remimazolam group was more sedated and took longer to recover to a RASS score similar to propofol. The frequency of application of vasoactive drugs during anesthesia was similar in both groups ($P = 0.119$). Despite rapid emergence with remimazolam after flumazenil reversal, re-sedation (10.8%) or somnolence (60%) in the PACU was observed, and the length of PACU stay in patients treated with remimazolam tosilate was longer than that of the propofol (35 min vs 30 min, $P<0.001$).

Conclusion: General anesthesia with remimazolam tosilate in conjunction with flumazenil reversal permits rapid recovery of consciousness in day surgery, but there was a notable occurrence of re-sedation or somnolence observed in PACU.

Keywords: remimazolam tosilate, flumazenil, propofol, day surgery, quality of recovery

Introduction

Along with the rapid development of the medical level and the popularity of the concept of enhanced recovery after surgery, day surgery has become a mature surgical management mode, widely carried out by many tertiary medical institutions in China. Day surgery is a medical mode of completing admission, surgery, and discharge within 24 hours or one day.[1] It has the characteristics of minor trauma, quick recovery, short hospitalization time, and maximizing utilization of medical resources, and it has gradually become the mainstream trend in hospitalized surgery. Based on the concept of rapid rehabilitation in day surgery, it is essential to select appropriate anesthetic drugs to permit the patient to undergo

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a procedure with minimum stress and maximum comfort to enable early discharge without sequelae,[2] which poses a severe challenge to anesthesia management. Due to the broadening of the scope of day surgery, the patient population and surgical types have gradually become complicated, and new sedative drugs have emerged in anesthesia management.

Remimazolam tosilate is a novel ultrashort-acting benzodiazepine that was obtained by Jiangsu Hengrui Pharmaceutical Company through the salt modification of Remimazolam.[3] It is an innovative chemical drug that contains many outstanding advantages, like rapid onset and offset, few hemodynamic side effects, minimal nephrotoxicity and hepatotoxicity, and no esterase metabolism as well as accumulation,[4] which has been successfully marketed in China. The good sedative effect and safety in general anesthesia with remimazolam have been confirmed in many researches.[5–7] Furthermore, like another benzodiazepine, remimazolam's effect can be reversed by flumazenil,[8,9] which is not possessed by the classical sedative propofol.[10]

Despite the lower surgical trauma and anesthesia risk of patients receiving day surgery than traditional surgery, it is difficult to fully observe their postoperative recovery profiles due to the short hospitalization. Thus, improving the quality of early postoperative recovery and driving to reduce the length of stay are crucial for day surgery with limited observation time.[10] Remimazolam has a short history of use in total intravenous anesthesia (TIVA), so limited information is available about its properties related to the early postoperative quality compared with the classical sedative propofol.[11] It is, therefore, vital to analyze the quality of earliest recovery in individuals who experienced general anesthesia with the remimazolam. Propofol was used in the control group.

Our study utilized the revised Mandarin version of PostopQRS to evaluate the quality of patients' postoperative recovery.[12] The revised Chinese version of the PostopQRS questionnaire was validated as efficient and reliable as the original English version, which tracks multiple domains of recovery from immediate to long-term time periods in patients.[13] The PostopQRS scale was measured in six dimensions: overall recovery, physiological (9 items), nociceptive (2 items), emotive (2 items), activities of daily living (4 items), and cognitive recovery (5 items). Recovery was assessed at multiple time periods before and after surgery. The recovery outcome is a binary classification, defined as returning to at least baseline values. This is a feasible survey-based tool that provides reliable results via face-to-face or telephone interviews. Therefore, our research is dedicated to evaluating the quality of recovery by assessing the PostopQRS in both groups to providing a reference experience for the selection of anesthesia protocol for day surgery.

Materials and Methods
Study Design and Ethics
From March 2023 to October 2023, we carried out a single-blinded randomized clinical study that was authorized by Lianyungang Clinical College of Nanjing Medical University Ethics Committee (KY -20230313002-01). The study was registered before enrollment at the Chinese Clinical Trials Registry (ChiCTR2300069933, 29 March 2023). All patients provided written informed consent prior to participation. This study complied with the 1964 Helsinki Declaration and its later amendments.

Patients
This trial enrolled male and female patients aged 18 to 65 years old who had an American Society of Anesthesiologists (ASA) physical status of I or II, a body mass index (BMI) of 18 to 30 kg/m^2, and were scheduled for day surgery with tracheal intubation for less than 2 hours. The exclusion criteria included pregnant or breast-feeding women and those who had a delivery plan within 3 months; significant cardiorespiratory instability and renal or hepatic dysfunction; severe neuropsychiatric disorders and cognitive dysfunction; use of opioids or benzodiazepines within the last month; as well as those who have a history of allergies or contraindications to study drugs.

The preoperative cognitive function in this study was assessed using the Chinese Mini-Mental Status (CMMS), which is a 30-point examination revised by the Mini-Mental State Examination (MMSE) and adapted to Chinese culture.[14] We used the scoring and adjusted for the patient's educational level as a proxy for preoperative dementia ($\leq$ 24 with an

educational level of secondary education, or CMMS ≤ 20 with an educational level of primary education, or CMMS ≤ 17 with an educational level of illiteracy).[15]

Randomization and Blinding

Eligible participants were randomized to receive remimazolam tosilate (intervention) or propofol (control) in a 1:1 ratio using the random number generated by the web (https://www.random.org/). Both patients and surgeons were blinded to the allocation, but the anesthesiologist was not blind since they needed to administer the medication accordingly.

Interventions

No premedication was administered to any of the enrolled individuals. Upon arriving at the operating room, routine monitoring was carried out, which included the electrocardiogram, pulse oxygen saturation (SpO_2), non-invasive blood pressure (NIBP), train-of-four (TOF), nasopharyngeal temperature, and the bispectral index (BIS).

For induction of anesthesia, an initial intravenous administration of remimazolam tosilate (0.3 mg/kg, iv) (Jiangsu Hengrui Pharmaceutical Co., Ltd, China) or propofol (2–2.5 mg/kg, iv) (Beijing Fresenius Kabi Pharmaceutical Co., Ltd, China) was administered for sedation. A minute later, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) was performed. After the score was 3 or less, 0.3–0.5 μg/kg of sufentanil and 0.08–0.1 mg/kg of neuromuscular blocking agent vecuronium were administered to patients. Alternatively, an additional dosage of remimazolam tosilate (0.05 mg/kg) or propofol (0.5 mg/kg) would be administered until MOAA/S≤3. After the induction of anesthesia, patients underwent intubation and were then mechanically ventilated with a tidal volume of 6–8 mL/kg. The respiratory frequency was adjusted to ensure that the end-tidal carbon dioxide concentration remained within the range of 35–45 mmHg. All patients received dexamethasone (5 mg) and dolasetron (12.5 mg) after induction for anti-emetic prophylaxis, respectively.

Anesthesia was maintained with remimazolam (1–1.5 mg/kg/h) or propofol (4–8 mg/kg/h), and continuous infusion of remifentanil (0.2–0.3 μg/kg/min) was used in both groups for analgesia. The depth of sedation was monitored with BIS and medications were titrated to keep the BIS range between 40 and 60. Vasoactive agents were administered accordingly to maintain the blood pressure within 20% of the baseline value. Sinus bradycardia, defined as a heart rate below 40 beats per minute, was treated with 0.5 mg of atropine. During the procedure, the maintenance infusion dose of sedative was adjusted according to the BIS. If the maximum dose of the study drug was insufficient to sedate, additional remimazolam 0.05 mg/kg or propofol 0.5 mg/kg were administered at 2-minute intervals, respectively. If adequate sedation were still not achieved after two consecutive administrations of the additional dose, the subject would be excluded, and combined intravenous and inhalation anesthesia would be used. If the BIS remained inside the target sedation depth, the infusion rate of remifentanil could be increased or decreased based on the vital signs.

Towards the end of the operation procedure, intravenous anesthesia was stopped and muscle relaxant antagonism was used. If the TOF count ≤ 2, 4 mg/kg of sugammadex was administered, and otherwise, 2 mg/kg of sugammadex was given,[16] then patients were transferred to the PACU for recovery. Five minutes after the end of the surgery, flumazenil 0.5 mg was used in the remimazolam tosilate group in the PACU. The dosage of flumazenil was determined following the phase Ib clinical trials of remimazolam undergoing colonoscopy.[17] Tracheal extubation was performed after confirming the recovery of consciousness and sufficient spontaneous breathing. In the PACU, tramadol 50 mg or metoclopramide 10 mg were given if the visual analog scale (VAS, ranging from 0 to 10) score of pain or nausea/vomiting exceeded 4. Patients were allowed to leave the PACU when the post-anesthesia discharge score was at least 9.

Outcome Variables

The primary outcome of interest in our trail was the incidence of overall recovery evaluated by the Chinese version of the PostopQRS questionnaire on POD1. The overall recovery is defined as the recovery on all items of the scale. All patients were required to complete the PostopQRS five times: before the procedure (baseline), 15 min and 40 min after surgery, and POD1, POD3. The recovery outcome is a binary classification that refers to a return to baseline values or better.

Secondary outcomes included: recovery of each PostopQRS domain across all time points over 3 days; the RASS scores in the PACU; time of tracheal extubation; time to fully alert and the duration of PACU stay; application of

vasoactive drugs during anesthesia; adverse events throughout anesthesia and recovery; as well as patient and anesthesiologist satisfaction (assessed on a 4-point scale, 1 represents not satisfied and 4 represents very satisfied). Among them, the evaluation time points of the RASS score included upon emergence, at 5 min, 15 min, and 30 min after eyes-opening. Fully alert was defined as the patient accurately stating their name and date of birth in a normal tone. Adverse events during the study period were recorded, which included nausea and vomiting, intraoperative awareness, re-sedation, and somnolence. Intraoperative awareness was assessed with a modified Brice interview. In our trial, re-sedation was defined as a decrease in the RASS score of 1 or more. Somnolence was regarded as a constant state of sleepiness that can be awakened and responded to correctly but falls asleep again quickly when the stimulation is removed. The PACU discharge criteria were defined as the modified Aldrete score of at least 9.[18]

Statistical Analysis

Sample size estimates were based on preliminary testing at our institution. According to our pre-trial, the overall recovery of the PostopQRS on POD1 in the remimazolam group was approximately 45.3%, and the overall recovery was 69.4% on POD1 in the propofol group.

Assuming an alpha error of 0.05 and a power of 80% (two-sided tests), a sample of 126 participants was required by calculation using the PASS 15 software. Considering an anticipated dropout rate of 10%, 140 patients were finally enrolled in our trial.

All data were presented as mean (SD), median (interquartile range, IQR), or number (percentage) as appropriate. The normality of quantitative variables was assessed using the Shapiro–Wilk test. For comparison of the differences between the groups, continuous data were analyzed using the Student's t-test or the Wilcoxon rank-sum test based on the distribution, and the qualitative variables were analyzed using the Chi-square test or Fisher's exact test as needed.

Each of the recovery domains of the PostopQRS was assessed using a generalized estimation equation (GEE), which represents the interaction between time and group. All analysis was evaluated using a two-tailed test, and a P value below 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 26.0 and GraphPad Prism 8.0.

Results

Patient Demographic and Clinical Characteristics

A total of 140 participants were screened, of whom 3 were excluded and 137 patients were randomized into two groups: 69 to the remimazolam tosilate group and 68 to the propofol group. Later, six patients discontinued the intervention due to a breach of our protocol, and three patients did not receive follow-up because of a loss of telephone contact with them. Thus, 128 participants were ultimately analyzed in this research. The full details are shown in the flow diagram (Figure 1). The characteristics of patients and surgeries are shown in Table 1. There were no relevant imbalances in the baseline demographic characteristics of the two treatment groups (P > 0.05; Table 1).

Primary Outcome

The overall and subdomain recovery of the PostopQRS are illustrated in Figure 2. Although there was some difference in the overall recovery rate of PostopQRS on POD1, it did not differ significantly between groups (remimazolam 47.7% vs propofol 65.1%; OR 0.52; 95% CI 0.26 to 1.06; P = 0.072). In general, the overall recovery of the PostopQRS increased over time, and its interaction between time and group was significant (P = 0.003).

Secondary Outcomes

The five dimensions that differed between the two treatment groups are presented in Figure 2. Among the five dimensions of the PostopQRS, there were similarities in the recovery including nociception and activities of daily living. Physiological support was comparable between the groups. On the whole, the physiological recovery of the PostopQRS increased over time, and its interaction between time and group was significant (P = 0.032). Besides, emotional state and cognitive recovery in the remimazolam group were significantly decreased compared with the control group (P < 0.001
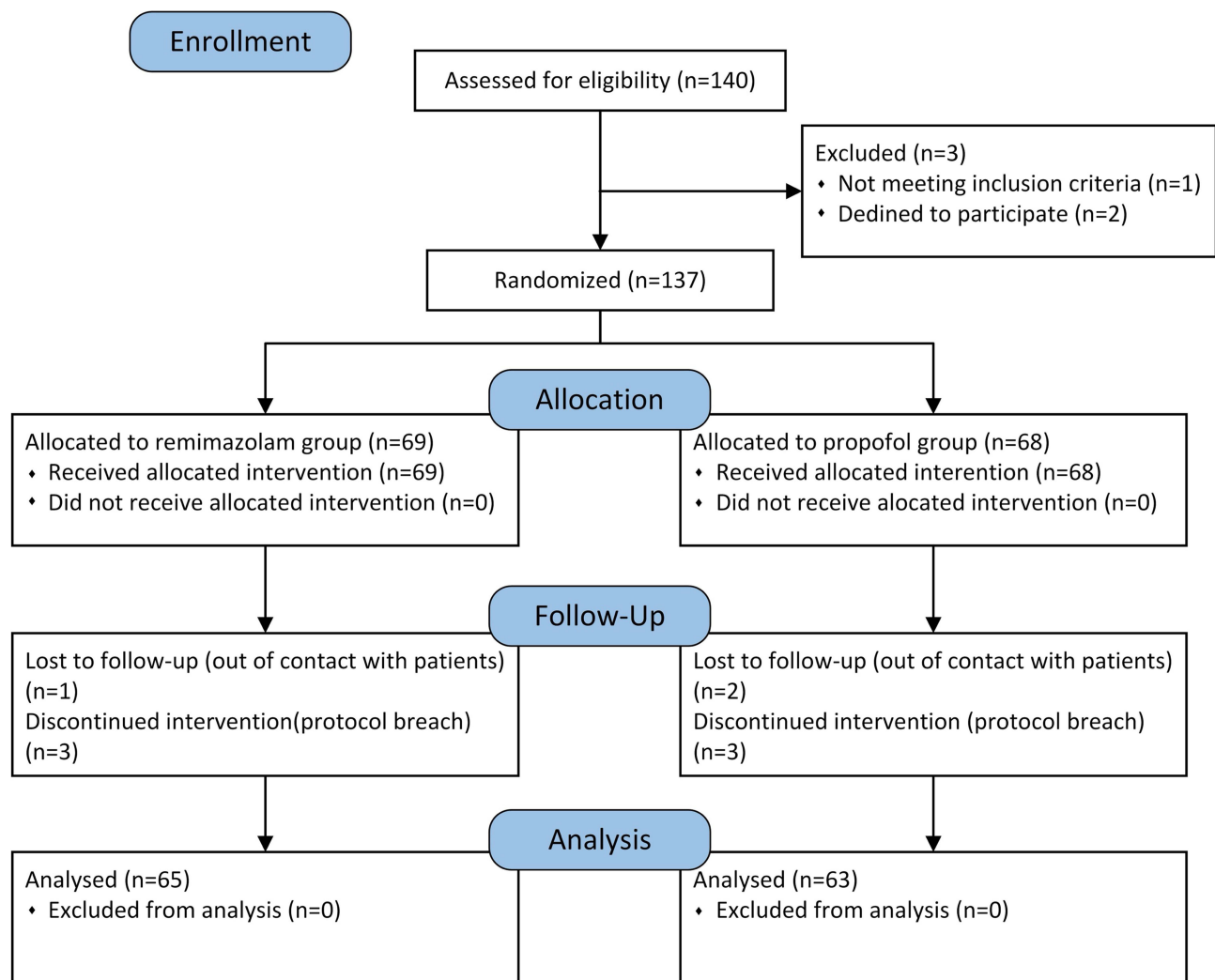
Figure 1 CONSORT 2010 flow diagram.

for each), and the changes over time were significantly different between the groups. Neither group exhibited post-operative delirium before PACU discharge and on POD 1 and POD 3. There were no differences between the two groups in the face-to-face and telephone interviews for cognitive status on POD 1 (OR = 0.508; P = 0.584) and POD 3 (OR = 0.676; P = 0.678).

Intraoperative data, including the BIS value, the total amount of anesthetic drugs, and the application of vasoactive medicines during anesthesia are shown in Table 2. The duration of anesthesia and the operation were comparable

Table 1 Baseline Demographic Characteristics of the Participants

Variables	Remimazolam (N=65)	Propofol (N=63)	Mean Difference (95% CI)	Value
Age, years	49.08±9.40	47.63±10.16	−1.44 (−4.86 to 1.98)	0.406
Sex, n(%)				0.593
Male	33 (50.8)	29 (46.0)		
Female	32 (49.2)	34 (54.0)		
Height, cm	168.34±7.27	169.67±7.14	1.33 (−1.19 to 3.85)	0.299

(*Continued*)

Table 1 (Continued).

| Variables	Remimazolam (N=65)	Propofol (N=63)	Mean Difference (95% CI)	Value
Weight, kg	68.96±8.95	68.37±8.00	−0.60 (−3.57 to 2.38)	0.692
BMI, cm/kg^2	24.23±1.98	23.73±2.30	−0.50 (−1.25 to 0.25)	0.189
CMMS score	25.18±2.07	25.56±2.03	0.37 (−0.36 to 1.09)	0.308
ASA physical status, n (%)				0.110
I	30 (46.2)	38 (60.3)		
II	35 (53.8)	25 (39.7)		
Education level, n (%)				0.423
Elementary school and below	17 (26.2)	20 (31.7)		
Primary school	30 (46.2)	17 (27.0)		
Secondary school	14 (21.5)	16 (25.4)		
College and above	4 (6.2)	10 (15.9)		
Preoperative PostopQRS score	74.09±3.86	73.70±4.37	−0.39 (−1.83 to 1.05)	0.589
Surgical type, n (%)				0.827
Laparoscopic-cholecystectomy	22 (33.8)	22 (34.9)		
Internal fixation removal				
Upper limbs	12 (18.5)	13 (20.6)		
Lower limbs	13 (20.0)	11 (17.5)		
Endoscopic cordectomy	18 (27.7)	17 (27.0)		

Notes: Data were presented as the mean±SD, or number (percentage), as appropriate. The mean difference (95% CI) was the difference of the mean between the groups. No statistically significant differences between groups were noted.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; CMMS, Chinese Mini-Mental Status; PostopQRS, Postoperative Quality of Recovery Scale.

between the two groups. During the induction of anesthesia, the injection pain of propofol was higher than in the remimazolam group (39.7% vs 12.3%, P<0.001). However, the incidence of hiccups was significantly higher in the remimazolam group than in the control group (41.5% vs 1.6%, P<0.001). The frequency of vasoactive drug application during anesthesia became similar between the two groups (60.0% vs 73.0%, P = 0.119). That can be attributed to the frequent use of norepinephrine in the propofol group, while more antihypertensive drugs were used in the remimazolam group to maintain hemodynamic stabilization intraoperatively.

Postoperative data of the participants in the PACU were presented as median (interquartile range) or number (percentage) in Table 3. During the recovery period, all patients in the remimazolam group received flumazenil 0.5 mg. Consequently, time to eyes-opening, tracheal extubation, and full alert was statistically shorter in the remimazolam group (P<0.001 for all comparisons; Table 3). However, the median time in the PACU stay was significantly longer in the remimazolam group than in the propofol group (35 min vs 30 min, P<0.001).

Regarding the RASS score in the PACU, the RASS score upon emergence differed significantly between the two groups (0 [−1, 0] in the propofol group vs −1 [−1, 0] in the remimazolam group, P<0.001). This difference disappeared at 30 min after eyes-opening (0 [−1, 0] in the propofol group vs 0 [−1, 0] in the remimazolam group, P = 0.086), which represents that patients have returned to a vigilance and calm state. In terms of the satisfaction of the anesthesiologist with the intraoperative anesthesia management as well as postoperative emergence profiles, propofol was better than remimazolam tosilate (P < 0.001). In contrast, there was no significant difference observed in patient satisfaction (P = 0.123).
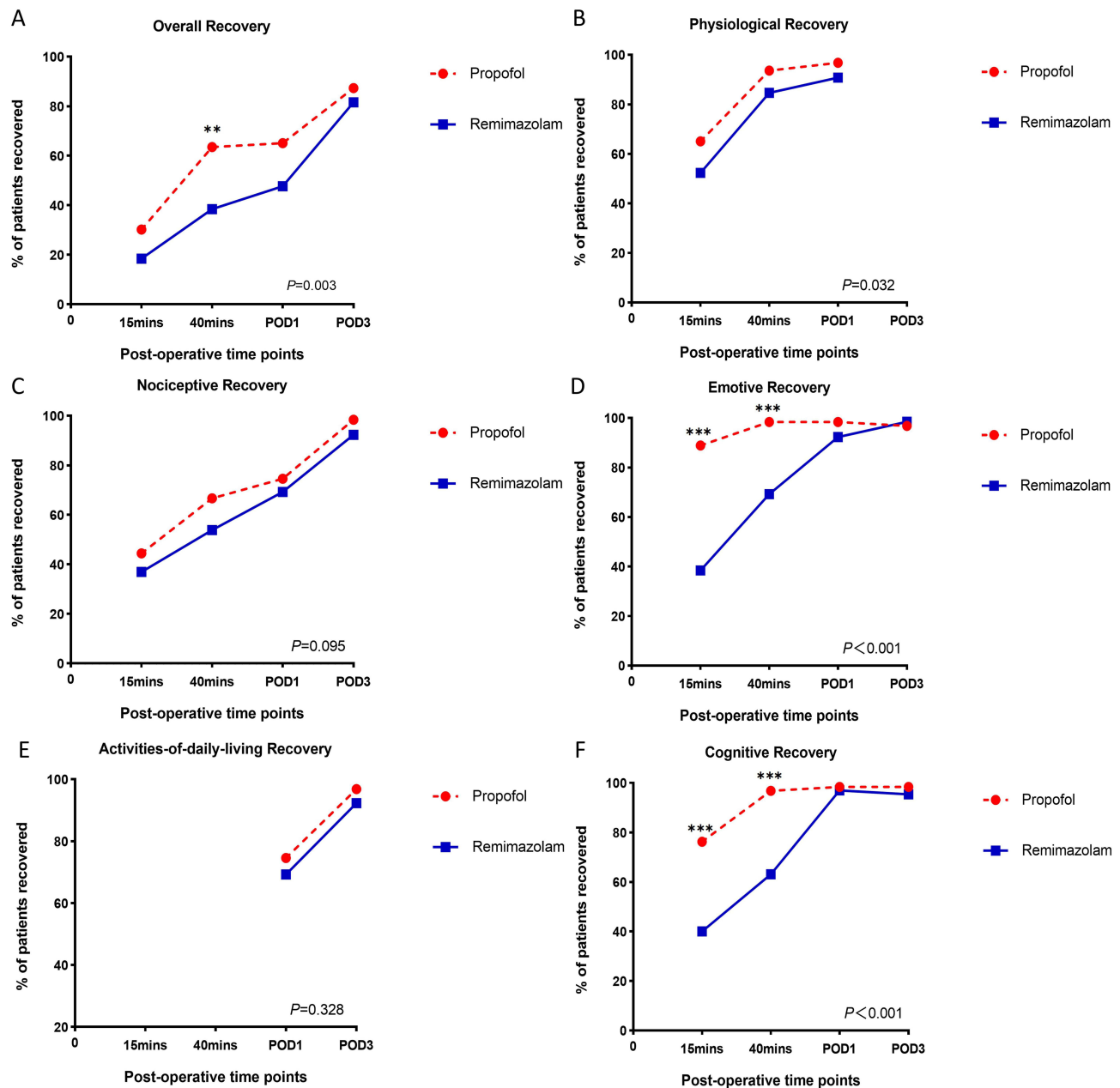
Figure 2 Postoperative recovery variation of the domains over time between the remimazolam group and the propofol group.
Notes: Data are presented as number (%), **P less than 0.01, ***P less than 0.001. The domains include (**A**) overall recovery (recovery on all items of the scale), (**B**) physiological recovery, (**C**) nociceptive recovery, (**D**) emotive recovery, (**E**) activities-of-daily-living recovery, and (**F**) cognitive recovery. P values were derived from GEE and represent the time by treatment interaction.
Abbreviation: GEE, generalised estimation equation.

Adverse Events

The detailed postoperative complications related to the study medications in PACU are recorded in Table 3. No patient had a severe adverse event. The incidence of postoperative nausea and/or vomiting was comparable between the two groups. Seven patients (10.8%) with remimazolam tosilate sedation were observed with re-sedation in the PACU, 3 of whom experienced a decrease in oxygen saturation due to respiratory depression. They can return even surpass the initial RASS score under external stimulation. Somnolence was observed in both groups during the post-procedural study period, but the incidence of somnolence was significantly lower in the propofol group (39 [60%] vs 7 [11.1%], P<0.001). No cases of intraoperative awareness were reported in this study. It is worth noting that 4 patients (6.2%) in the

Table 2 Intraoperative Data of the Participants

Variables	Remimazolam (N=65)	Propofol (N=63)	Value
Duration of anesthesia, min	48.98±18.32	46.44±15.22	0.056
Duration of operation, min	42.32±16.70	37.41±13.77	0.053
Total amount of anesthetic drug, mg			
Propofol	–	426.0[352.0 to 486.0]	
Remimazolam	82.0 [55.9 to 94.6]	–	
Injection pain, n (%)	8 (12.3)	25 (39.7)	<0.001
Hiccup, n (%)	27 (41.5)	1 (1.6)	<0.001
Total amount of remifentanil, mcg	566.0 [426.0 to 684.0]	479.0 [375.5 to 542.5]	0.003
Total amount of sufentanil, mcg	25.0 [22.5 to 25.0]	25.0 [25.0 to 25.0]	0.443
Total amount of vecuronium, mg	6.0 [6.0 to 8.0]	7.0 [6.0 to 8.0]	0.520
Need of vasoactive drug, n (%)	46 (73.0)	39 (60.0)	0.119
Total amount of norepinephrine, mcg	0.0 [0 to 16]	16.0 [0 to 40]	<0.001
Total amount of atropine, mg	0.0 [0 to 0]	0.0 [0 to 0]	0.162
Total amount of urapidil, mg	0.0 [0 to 20]	0.0 [0 to 0]	0.001
Mean BIS during intraoperation	53.3 [50.02 to 53.33]	48.8 [45.73 to 52.11]	<0.001
Fluids administered, ml	700.0 [600.0 to 800.0]	700.0 [475.0 to 800.0]	0.129

Note: Data were presented as the mean±SD, or number (percentage), or median [interquartile range], as appropriate.
Abbreviation: BIS, bispectral index.

Table 3 Postoperative Data of the Participants in the PACU

Variables	Remimazolam (N=65)	Propofol (N=63)	Value
Time to eyes-opening, min	7.0 [6.5 to 8.0]	12.0 [11.0 to 14.0]	<0.001
Time to extubation, min	7.0 [7.0 to 8.0]	13.0 [11.0 to 14.0]	<0.001
Time to fully alert, min	9.0 [7.5 to 11.5]	14.0 [12.0 to 15.0]	<0.001
Duration of PACU stay, min	35.0 [30.0 to 45.0]	30.0 [30.0 to 33.0]	<0.001
Adverse events in PACU, n (%)			
Nausea and /or Vomiting	6 (9.2)	7 (11.1)	0.725
Somnolence	39 (60.0)	7 (11.1)	<0.001
Re-sedation	7 (10.8)	1 (1.6)	0.033
Intraoperative awareness	0 (0.0)	0 (0.0)	1.000
Others	13 (20.0)	2 (3.2)	0.003

(*Continued*)

Table 3 (Continued).

Variables	Remimazolam (N=65)	Propofol (N=63)	Value
Maximal VAS pain score (0–10)	2.0 [2.0 to 3.0]	3.0 [2.0 to 3.0]	0.103
RASS score in the PACU			
Upon emergence	−1 [−1–0]	0 [−1–0]	<0.001
After 5 min	−1 [−1–0]	0 [0–0]	<0.001
After 15 min	0 [−1–0]	0 [0–0]	<0.001
After 30 min	0 [0–0]	0 [0–0]	0.086
Patient Satisfaction			0.123
1	0 (0.0)	0 (0.0)	
2	3 (4.6)	3 (4.8)	
3	20 (30.8)	11 (17.5)	
4	42 (64.6)	49 (77.8)	
Anesthesiologist satisfaction			<0.001
1	13 (20.0)	4 (6.3)	
2	17 (26.2)	3 (4.8)	
3	16 (24.6)	12 (19.0)	
4	19 (29.2)	44 (69.8)	

Note: Data were presented as median [interquartile range], or number (percentage), as appropriate.
Abbreviations: PACU, Post-anesthesia Care Unit; VAS, Visual Analogue Scale; RASS, Richmond Agitation-Sedation Scale.

remimazolam tosilate group experienced sweating. Their body temperature was normal and they needed rehydration therapy in the recovery phase. The reason may be the side effects related to flumazenil.

Discussion

In this trial, we compared the early postoperative recovery of patients undergoing day surgery with remimazolam tosilate versus propofol. Here, we used the PostopQRS scale to assess the postoperative recovery's quality. It is an efficient and reliable method to assess recovery after anesthesia and surgery. The propofol sedation did not show any significant differences from the remimazolam sedation in the overall recovery of PostopQRS on POD1. This result indicates that remimazolam-based TIVA is able to provide a similar quality of recovery to that of propofol when patients are discharged.

A prior work reported that the quality of postoperative recovery after remimazolam sedation was similar with propofol,[16] and this conclusion is consistent with our trial results. In our research, despite the favorable sedation and recovery profiles of remimazolam, some potential side effects still deserve the attention of anesthesiologists in the perioperative period. The patient's early recovery following surgery can be directly or indirectly impacted by these potential adverse effects. Therefore, regarding the reasons for the poor postoperative recovery in the remimazolam group in PACU, we also analyzed them and found that they mainly focused on cognitive ability and emotional state. Benzodiazepines are a reported risk factor for cognitive dysfunction.[19] We found a temporary decrease in cognitive function at 15 min and 40 min after surgery, while there was no significant difference at POD1 and POD3 between the groups. The cognitive function decline during the emergence after remimazolam anesthesia was not reported in other studies because the first assessment of cognitive function in their trial was mainly at POD1,[20] which led to an

underestimation of the effect of remimazolam on cognitive function. Remimazolam is another "soft drug" after remifentanil. Similarly, when the dose is at the top of the response curve, adverse desensitization effects and rebound phenomena might occur once the drug is stopped, thus inducing anxiety and depressive feelings.[21] Furthermore, the elimination half-life of remimazolam was about 45 min, which would explain why the differences in cognitive function and emotional state disappeared at POD1 and POD3.

Day surgery anesthesia is performed on patients who are hospitalized for 24 hours during their surgery. Perioperative complications in day-case anesthesia should be minimized, such as postoperative nausea and vomiting (PONV), post-operative behavioral disturbances, and cardiorespiratory complications. The choice of anesthetic agents can influence the occurrence of these complications thus delaying discharge. Therefore, short-acting anesthetics are needed in order not to compromise recovery after day surgery.[11] Propofol is the most classic TIVA agent, consistently associated with a quick early recovery. As a result of its favorable recovery profile, propofol occupies a major position in day-case surgery anesthesia.[22] Remimazolam, a new drug, is widely used in the field of sedation. The presence of a specific antagonist makes this sedative effect more controllable. Remimazolam has been previously reported to delay recovery but to achieve rapid and complete recovery with flumazenil.[5] In this regard, remimazolam combined with flumazenil may offer an additional means of "fast-tracking" recovery. Although a faster recovery of consciousness and significantly less time to fully alert from remimazolam-based TIVA could be achieved with the routine use of flumazenil as compared to propofol, longer somnolence after removing the endotracheal tube and a longer time to return to the higher RASS scores as well. Therefore, somnolence or re-sedation is still an undesired trouble that the anesthesiologist should pay attention to after flumazenil routinely reverses the sedation effect of remimazolam.

To prevent the occurrence of intraoperative awareness, we used BIS for each patient in this study. Mean BIS remained within the target range in both groups. We found that participants who received remimazolam tosilate had higher BIS values than those who received propofol intraoperatively, though at the same sedation level assessed by MOAA/S, which is in line with a previous report.[5] This may be attributed to the BIS being produced mainly based on data derived from the electroencephalograph of propofol and thus more sensitive to it. The reliability of the BIS value to monitor sedation depth during anesthesia with remimazolam has been controversial. The infusion rate of intraoperative anesthetic drugs was adjusted according to the BIS value, which may cause excessive doses of benzodiazepines, resulting in delayed recovery or decreased quality of emergence. Currently, the appropriate index to reflect the depth of sedation during remimazolam-based TIVA is not determined, and further exploration of it is necessary in the future.

The safety of flumazenil for reverse benzodiazepine sedation has been demonstrated.[11] Adverse events linked to flumazenil or remimazolam were documented in our study. Unlike previous studies, we similarly observed injection pain in the remimazolam group during anesthesia induction, although the incidence was lower than that in the propofol group. Moreover, it is no less painful than propofol in terms of the grade of the injection pain. In addition, this is also an issue that anesthesiologists cannot ignore that the use of remimazolam has been repeatedly reported to cause severe and rare allergic reactions, especially when the infusion rate is fast, and the exact mechanism of sensitization is currently unknown.[23,24] So remimazolam should be infused slowly, and timely treatment is required once allergies occur. The side effects caused by flumazenil may include seizures, arrhythmia, injection pain, sweating or shivering, headache, nausea, vomiting, anxiety, and so on.[25] Four patients or nine patients in the remimazolam group experienced sweating or headache during recovery from anesthesia, respectively, and gradually recovered with time without serious adverse events. All enrolled patients were routinely followed up before discharge, and all met the discharge criteria.

Flumazenil is effective in reversing the sedative and hypnotic properties of remimazolam and facilitating the recovery of consciousness after anesthesia. Therefore, when we used flumazenil, the patients were able to open their eyes quickly. However, there is still the problem that patients rapidly fall asleep again when external stimulation is lacking. In our trial, seven patients (10.8%) were observed with re-sedation in the PACU. Re-sedation refers to a decrease in the RASS score of 1 or more. All of these patients could recover or surpass the initial RASS score under external stimulation, so no additional flumazenil was given. Among them, three of the re-sedation patients experienced a decrease in oxygen saturation due to respiratory depression. Thirty-nine patients (60%) experienced drowsiness in the remimazolam group, which is the leading cause of prolonged residence time in PACU. None of the patients in our study developed re-sedation after returning to the ward. To date, there is no consensus on the dosage or timing of flumazenil administration

in patients who received remimazolam in combination with flumazenil. Consequently, further studies need to be performed to facilitate recovery in patients undergoing day surgery.

Nevertheless, there are several limitations in this trial. First, patients over 65 years old were not included in this study and the observed results may not apply to the more aging population. Second, the plasma concentration of remimazolam at the administration of flumazenil was not collected, so it is unclear whether a fixed dose of flumazenil (0.5 mg) is insufficient or excessive for different patients. An inadequate amount of flumazenil may cause delayed recovery or a reduced quality of emergence. Conversely, overdose will increase the incidence of adverse events. Furthermore, studies have shown that a recovery time similar to propofol can be achieved only when patients receive flumazenil 10 minutes after remimazolam cessation.[11] However, there has yet to be a definite consensus about the best time to treat with flumazenil after remimazolam discontinuation. Third, we only selected three different short-term procedures, so the type of surgery is relatively narrow and may not be generalized to other kinds of day surgery. Fourth, We are unsure whether the depth of anesthesia in the remimazolam group was optimal throughout the procedure because the accuracy of the BIS has not yet been determined. Therefore, suitable alternative tools are needed to measure the anesthesia depth of remimazolam.

Conclusion

In summary, we found that remimazolam tosilate combined with flumazenil permits a more rapid recovery of consciousness compared to propofol. Nevertheless, a significant percentage of participants in the remimazolam group experienced re-sedation and somnolence, although without any severe consequences. Remimazolam tosilate exhibited a superior safety profile compared to propofol in terms of hypotension, but the relatively stable hemodynamics of remimazolam came at the expense of more adverse effects. Hence, anesthesiologists should be aware of the risks of this narcotic. Protocols for optimizing the quality of the recovery profile after remimazolam tosilate anesthesia remain to be explored to allow for the fastest recovery.

Abbreviations

PostopQRS, postoperative quality of recovery scale; POD, postoperative day; RASS, Richmond Agitation-Sedation Scale; PACU, post-anesthesia care unit; TIVA, total intravenous anesthesia; ASA, American Society of Anesthesiologists; BMI, body mass index; MMSE, Mini-Mental State Examination; CMMS, Chinese Mini-Mental Status; SpO_2, pulse oxygen saturation; NIBP, non-invasive blood pressure; TOF, train-of-four; BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; GEE, generalized estimation equation; PONV, postoperative nausea and vomiting.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author upon reasonable request. An unauthorized version of the Chinese MMSE was used by the study team without permission. This issue was rectified between the authors and PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

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Disclosure

The authors declare no conflicts of interest in this study.

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