Rapid Alertness: A Popensity-score matched, Prospective Observational Study of Remimazolam vs. Propofol Infusion for Sedation in Spinal Anesthesia Non-healthy Patients

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Abstract

Objectives: The demand for procedural sedation is increasing, with propofol remaining a popular choice due to its safety and rapid recovery profile. Remimazolam presents a promising alternative, offering a rapid onset and short duration of action. Its favorable safety profile and suitability for continuous infusion make it particularly advantageous. This study aimed to evaluate recovery times following continuous infusion of remimazolam compared to propofol sedation.

Methods: From February to June 2023, we conducted a single-center, prospective, observational study approved by the Sestre milosrdnice University Hospital Center Ethics Committee. Ninety ASA II or III patients undergoing infraumbilical orthopedic, vascular, or inguinal hernia repair surgeries under spinal anesthesia were assigned to receive either remimazolam or propofol sedation. Sedation depth was assessed using Bispectral index (BIS), Modified Observer's Assessment of Awareness/Sedation Scale (MOAA/S), and Richmond Agitation and Sedation Scale (RASS). Sedation onset, duration, and recovery times were recorded, alongside dosage adjustments based on target BIS values of 60-80. Propensity score matching was employed to address confounding variables.

Results: Remimazolam exhibited significantly faster recovery times, with a median time to achieve BIS>80 of 3.0 min (IQR: 2.5), compared to 6.0 min (IQR: 3.0) for propofol, $p<0.001$. Remimazolam achieved satisfactory sedative and amnestic effects at a median continuous dose of 0.18 (0.1) mg/kg/h, with comparable sedation durations. Significant differences were noted in intraoperative memory retention: 40.0% of patients in the propofol group vs. 10.0 % in the remimazolam group reported memory of the event, $p=0.017$.

Conclusions: Remimazolam demonstrates superior recovery time and amnestic properties compared to propofol after continuous infusion sedation. Additionally, remimazolam matches or exceeds propofol in efficacy and safety for intraoperative sedation in non-healthy patients undergoing spinal anesthesia.
Keywords: Sedation; Propofol; Remimazolam; Spinal anesthesia; Bispectral index.

Introduction

Procedural sedation is recognized as a vital component adjunct to regional anesthesia, alleviating patients' anxiety, discomfort, and pain.[1] The growing demand for procedural sedation for patients undergoing regional anesthesia has become a clinical necessity, prompting the exploration and development of novel sedative agents that combine efficacy and safety. Intravenous sedatives such as midazolam, ketamine and dexmedetomidine have traditionally played a prominent role due to their sedative and anxiolytic properties and are routinely used in anesthesia and sedation. The downside of these drugs is their potential to cause unwanted side effects, such as hemodynamic instability, respiratory depression, or delayed awakening due to prolonged sedation after the procedure.[2,3] Propofol is a highly effective anesthetic for intraoperative and procedural sedation, known for its safety and rapid recovery times. It also leads to higher post-anesthesia recovery scores, better sedation, and improved patient cooperation.[4] However, propofol can cause respiratory depression, hemodynamic instability and pain on injection.[5]Additionally, with prolonged use it may lead to hypertriglyceridemia and the rare but serious propofol infusion syndrome (PRIS). It also lacks a specific reversal agent, and its metabolism depends on liver and kidney function, which may pose challenges in patients with organ dysfunction.[6]

Remimazolam has garnered considerable attention for its remarkable pharmacological profile characterized by rapid onset, ultra-short duration of action, and a favorable safety profile, making it a promising agent for procedural sedation.[7] In contrast to propofol, remimazolam offers more stable hemodynamics with a lower risk of hypotension and respiratory depression, particularly in vulnerable patients. It also has an available reversal agent (flumazenil), and a lower risk of injection pain or hypertriglyceridemia due to the absence of lipid content.[2,6] A recent study has shown that remimazolam is an effective sedative for cesarean section under spinal anesthesia, reducing the incidence and severity of intraoperative nausea and vomiting with minimal hemodynamic impact compared to midazolam, offering an additional clinical advantage.[8] Since it is metabolized by tissue esterase and has a context-sensitive half-time (CSHT) of 6–7 minutes, repeated bolus doses every 5 minutes are recommended.[9,10] A recent meta-analysis has shown that remimazolam has comparable efficacy and greater safety profile than propofol for sedation during gastrointestinal endoscopies.[11] Given that it has been shown that neither liver nor kidney dysfunction affects clearance, remimazolam can be safely used as a continuous infusion. To date, few studies have explored the safe use of remimazolam for continuous administration.[12]

The current literature includes limited number on the use of continuous remimazolam infusion for sedation, particularly in patients with increased anesthetic risk. We aimed to determine whether recovery times differ between continuous infusions of remimazolam and propofol. The secondary aim of this study was to determine the necessary range of continuous dose of remimazolam for procedural sedation, and to compare the performance in sedative and amnestic effects of continuous infusion of remimazolam and propofol, together with potential side effects for non-healthy (American Society of Anesthesiologists (ASA) II/III) patients.

Methods

This was a single-center study, conducted at Sestre milosrdnice University Hospital Center from February to June 2023, following approval by the institution's Ethics Committee (approval number 003-06/22-03-034). This was a prospective, observational clinical study, conducted in accordance with the Declaration of Helsinki. Written informed consent prior to participation was obtained from 90 consecutive patients (ASA II and III) who required sedation for surgical procedures under spinal anesthesia. Exclusion criteria included age under 18 or over 80 years, allergy to any of the drugs used, BMI under 18 or over 30 kg/m^2, psychiatric diagnoses and patient refusal.

Demographic and clinical data were recorded on a standardized form (age, sex, height and weight). Clinical data recorded before the start of the procedure were ASA status, bispectral index (BIS), Modified Observer's Assessment of Awareness/Sedation Scale (MOAA/S) and Richmond Agitation and Sedation Scale (RASS). This observational study included a total of 90 patients: 60 patients were sedated with remimazolam and 30 with propofol [Figure 1]. Patients received no premedication. Standard intraoperative monitoring was applied: noninvasive blood pressure (NBP), continuous electrocardiogram (ECG), and pulse oximetry (SpO_2). To assess the level of sedation during the procedure, the MOAA/S scale was used, with values 2-3 representing moderate sedation, considered adequate for the successful implementation of the procedure.[13] Additionally, the RASS scale was used as another validated tool for monitoring sedation depth, with target values ranging from -1 to -3.[14] BIS was used as a primary indicator of the depth of consciousness. All patients underwent surgery under spinal anesthesia. The procedures included infraumbilical orthopedic, vascular, and inguinal hernia repair surgeries. Spinal anesthesia was performed according to a standardized procedure and after satisfactory sensory and motor changes were established, additional anesthesia monitoring (BIS) was set up and MOAA/S and RASS scores were assessed. BIS, MOAA/S and RASS scale, infusion speed and duration, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and SpO2 were recorded every 5 minutes. Remimazolam and propofol induction doses, onset time of sedation and time to recovery were noted. The total doses of remimazolam and propofol, as well as the total sedation time, were recorded.

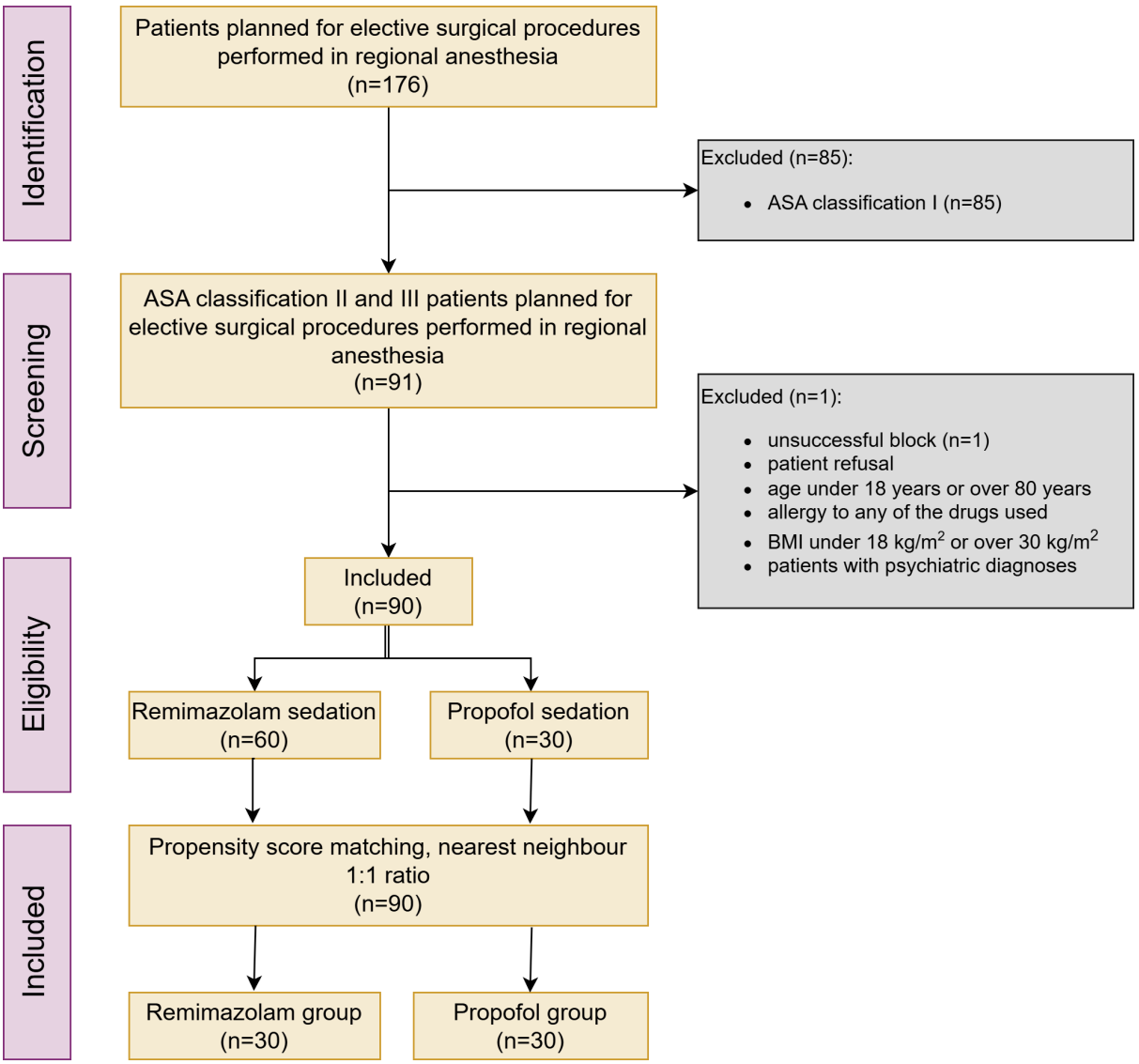

Figure 1: The Consolidated Standards of Reporting Trials (CONSORT) flowchart outlines the selection process for the study.

Recommended dosage of remimazolam for the induction of sedation is 5 mg intravenous (IV).[15] We started with the same initial dose of 5 mg IV bolus and measured time to BIS<80; if not reached, initial dosage of 2.5 mg IV was given. After induction continuous infusion was started from a syringe pump with 20 mg of remimazolam (Byfavo™ 20 mg powder for solution for injection) supplemented with 0.9% saline to 20 mL, to achieve 1 mg/ml dilution, with dose titration depending on BIS values. The initial propofol dose for reaching BIS values below 80 was 0.5 mg/kg IV (Propofol 10 mg/ml MCT Fresenius™), with further continuous dose titration depending on BIS values. The target BIS values were 60-80, which indicates moderate sedation, and infusions of the drugs were changed according to it, to avoid patients being either too awake or too deeply sedated. Onset time of sedation, defined as the time to reach value of BIS<80 for both drugs, were recorded. At the end of the procedure, after stopping the administration of the drug, the time to recovery (time required from the end of the infusion to the value of BIS>80; awake state) was measured. The total amount of remimazolam and propofol administered was recorded at the end of the procedure. Side effects: hypotension (systolic blood pressure below 90 mmHg), bradycardia (heart rate below 50 per minute), low blood oxygen saturation (SpO_2

below 90%), apnea (absence of breathing effort ≥10 seconds), memory of events (evaluated with Brice questionnaire, a tool used to assess awareness under anesthesia) and body movements during the operation, as well as the drugs used to treat side effects, were noted.

We estimated the required sample size based on the median recovery time, reported as 2.3 min (interquartile range, IQR: 1.8–3.3) for remimazolam and 5.0 min (IQR: 3.5–7.8) for propofol.[16] Based on these medians and considering a significance level of 0.05 and a power of 80%, we calculated an estimated minimum necessary sample size of 10 participants per group. Normality of the distribution of variables was tested using the Shapiro-Wilk test. Continuous variables are shown as mean±standard deviation or median (interquartile range), as appropriate. To adjust for the confounding factors, a propensity score matching with optimal match without replacement and 1:1 nearest neighbor method with logistic regression distance was used. The matching demographic and clinical variables included age, gender, BMI, ASA status, history of hypertension and diabetes, and initial BIS, MOASS, and RASS scores. The quality of the matching was assessed using the standardized mean difference where an absolute standardized mean difference of up to 0.1 was considered an excellent balance. In analysis after propensity matching, continuous variables are compared using t-test or Mann Whitney U test. Categorical variables are represented as number and corresponding percentage and differences tested with the $\chi 2$ test or Fisher's exact test for frequencies less than 5. For statistical analysis, Python (Centrum voor Wiskunde en Informatica, Amsterdam, the Netherlands) Statsmodels v. 0.14.0 and ScyPy v. 1.11.2 were used, and graphical representations were made using Python's Matplotlib v.3.5.2.[17] The data associated with the paper are not publicly available but are available from the corresponding author on a reasonable request.

Results

Ninety patients underwent spinal anesthesia with intraoperative sedation. Sixty patients were sedated with remimazolam and 30 patients with propofol. Before matching, 2 out of 9 features were unbalanced, however, after matching, all features were balanced. Following propensity score matching, there was no significant difference in the patients' demographic and initial clinical characteristics (Table 1).

Table 1: Demographic and initial clinical characteristics of the cohorts before and after propensity score matching.

	Before matching			**After matching**			
	Remimazolam (*n*=60)	**Propofol (*n*=30)**	**SMD**	**Remimazolam (*n*=30)**	**Propofol (*n*=30)**	**SMD**	***P* value**
Age, years	69.0 (19.0)	66.0 (15.7)	0.13	66.0 (18.5)	66.0 (15.1)	0.03	0.706.
Gender - male, n (%)	42 (70.0)	16 (53.3)	0.34	15 (50.0)	14 (46.7)	0.00	0.875.
BMI, kg/m^2	27.5 ± 3.8	25.8 ± 2.8	0.03	26.0 ± 3.0	25.2 ± 2.9	0.01	0.666.
Initial BIS	97.0 (3.0)	97.5 (3.0)	0.01	97.0 (3.0)	97.5 (3.0)	0.01	0.247.
Initial MOAA/S	5.0 (0.0)	5.0 (0.0)	0.01	5.0 (0.0)	5.0 (0.0)	0.01	0.923.
Initial RASS	0.0 (0.0)	0.0 (0.0)	0.00	0.0 (0.0)	0.0 (0.0)	0.00	0.657.
ASA							
II, *n* (%)	33 (55.0)	19 (63.3)	0.05	16 (53.3)	19 (63.3)	0.03	0.785.
III, *n* (%)	27 (45.5)	11 (36.7)		9 (30.0)	11 (36.7)		

Hypertensio *n* – yes, *n* (%)	28 (47.5)	17 (56.7)	0.04	14 (46.7)	16 (53.3)	0.03	0.797.
Diabetes type 2 – yes, *n* (%)	11 (19.0)	4 (13.3)	0.03	4 (13.3)	4 (13.3)	0.01	0.740.

BMI, body mass index; BIS, Bispectral index; MOAA/S, Modified Observer's Assessment of Awareness/Sedation Scale; RASS, Richmond agitation sedation scale; SMD, standardised mean difference;. Values are mean±standard difference, median (interquartile range) and number of patients (%).

In the matched cohort, the median time to the targeted BIS value was statistically significant, with 2.0 (2.0) min for remimazolam and 4.0 (10.0) min for propofol, p=0.026. Achieving BIS recovery above 80 was faster for remimazolam, at 3.0 min (IQR: 2.5) compared to 6.0 min for propofol (IQR: 3.0), p<0.001. There was no significant difference in infusion duration times or total sedation times (Table 2).

Table 2: Main outcome variables.

	Remimazolam (*n*=30)	**Propofol (*n*=30)**	***P* value**
Infusion duration (minutes)	51.5 (31.5)	37.5 (26.0)	0.786
Total sedation time (minutes)	42.5 (13.0)	42.0 (25.7)	0.228
Time from infusion start to targeted BIS value (minutes)	2.0 (2.0)	4.0 (10.0)	0.026
Time to BIS value recovery to >80 (minutes)	3.0 (2.5)	6.0 (3.0)	<0.001

BIS, bispectral index. Values are median (interquartile range).

The median continuous dose of remimazolam was 0.18 (0.1) mg/kg/h, while for propofol, it was 1.9 (0.1) mg/kg/h [Figure 2]. The doses applied resulted in moderate sedation range starting from the 5th minute onwards for all data points; BIS values (from 70 to 80) in 46.5% of time points, RASS scale (from -3 to -1) in 50.8% of time points, and MOAA/S scale (from 2 to 3) in 28.8% of time points [Figure 3].

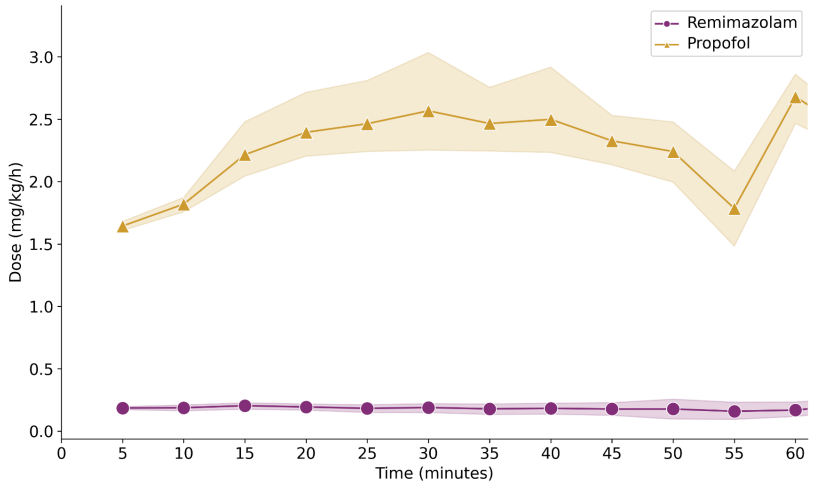

Figure 2: Continuous remimazolam and propofol doses applied.

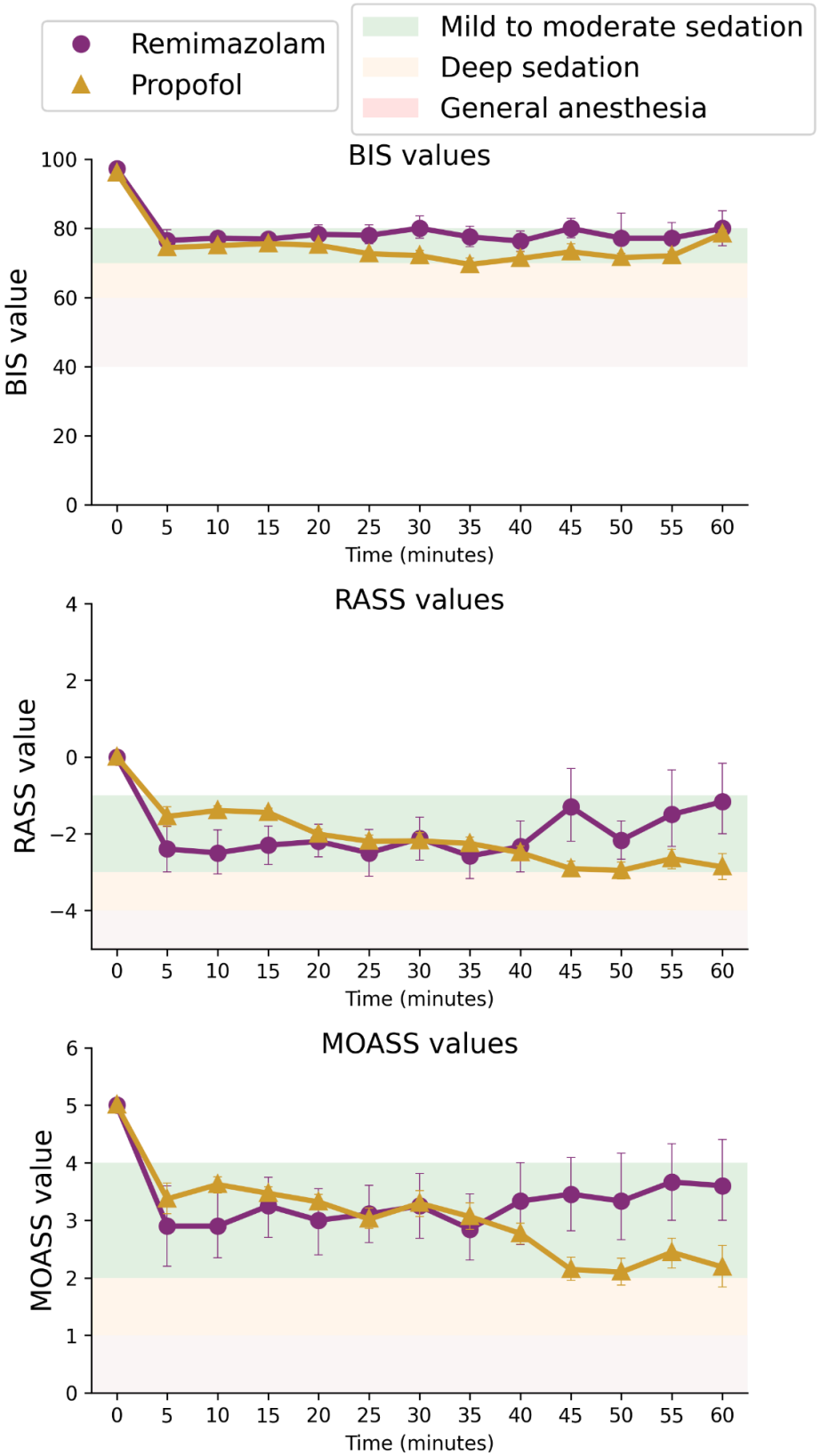

Figure 3: A comparison of achieved BIS (Bispectral index), RASS (Richmond sedation scale) and MOAA/S (Modified Observer's Assessment of Awareness/Sedation Scale) between remimazolam and propofol groups.

Regarding side effects, hypoxia was the predominant issue during propofol sedation, observed in 7 (23.3%) of cases, compared to 3 (10.0%) in the remimazolam group, but the difference was not statistically significant. Hypotension was the most prevalent side effect in the remimazolam group, occurring in 6 (20.0%) cases, compared to 3 (10.0%) in the propofol group, which was not statistically significant. There was no difference in the correction of hypotension with ephedrine between the two groups. Bradycardia was the least frequent side effect, observed only in two cases in the propofol group, with atropine used in only one case. No cases of bradycardia occurred in the remimazolam group (Table 3). The only statistically significant difference between the two groups was in memory of the event, with 12 (40%) patients in the propofol group and 3 (10.0%) patients in the remimazolam group reporting retention of the experience during the procedure (p=0.017).

Table 3: Incidence of side effects.

Variable	Remimazolam (*n*=30)	Propofol (*n*=30)	*P* value
Hypotension (n, %)	6 (20.0)	3 (10.0)	0.470
Ephedrine use (n, %)	4 (13.3)	2 (6.7)	0.667.
Bradycardia (n, %)	0 (0.0)	2 (6.7)	0.470.
Atropine use (n, %)	0 (0.0)	1 (3.3)	0.999.
Hypoxia (n, %)	3 (10.0)	7 (23.3)	0.299.
Apnea (n, %)	1 (3.3)	1 (3.3)	0.999.
Movement (n, %)	5 (16.7)	10 (33.3)	0.233
Memory of event (n, %)	3 (10.0)	12 (40.0)	0.017

Discussion

The main finding of this study is the statistically significantly faster recovery time after discontinuation of continuous remimazolam infusion compared to propofol. We observed that the recovery time for BIS values (achieving BIS >80) following remimazolam infusion was 3.0 min compared to 6.0 min for propofol. Additionally, we have determined that a continuous remimazolam infusion at a median dose of 0.18 mg/kg/h provided effective, satisfactory and safe sedative and hypnotic effects in non-healthy patients.

In recent years, numerous studies have explored remimazolam's potential for intraoperative sedation. However, few have investigated its continuous administration for sedation, especially in non-healthy individuals, and those that did often report inconsistent dosing regimens. The primary goal of our study was to determine whether there is a difference in recovery time between continuous infusions of remimazolam and propofol in non-healthy patients. The secondary aim was to identify an appropriate dosing range of remimazolam for intraoperative sedation and to confirm its efficacy and safety in non-healthy individuals.

A key finding of this study is the recovery time of BIS values following continuous infusion, where median time after cessation of remimazolam infusion to achieve BIS values above 80 was 3.0 min while for propofol group was 6.0 min (p<0.001). Previous studies have shown that remimazolam and propofol have similar CSHT, indicating only subtle differences in recovery time.[18] However, in a study using remimazolam for continuous sedation during impacted third molar extractions, the time to spontaneous eye opening was 8.0 min, similar to our findings, despite a higher infusion rate of 0.40 mg/kg/h.[19] A recent meta-analysis highlights the fact that the reported time to recovery varies greatly.[20] This meta-analysis, which included only studies on procedural sedation for short endoscopic procedures, also points out great discrepancy in results, attributed to

the inclusion of various patient populations, different procedural durations and complexities and a lack of reporting on relevant comparative safety or efficacy outcomes. Remimazolam does not exhibit cumulative sedative effects with increased duration of dosing up to 9 h under general anesthesia. However, changes in the infusion rate near the end of the procedure, difference in the BIS score at the end of infusion and female sex can result in up to 5 min difference in time to extubation.[21] Although a 3-minute difference in recovery time may seem small, it can be important in everyday clinical practice, especially in busy hospitals. In high-volume surgical settings, even small time savings can add up, helping operating rooms run more efficiently, reducing time in the recovery area (PACU), and keeping schedules on track. Faster recovery also means patients spend less time under sedation, which can lower the risk of complications such as airway problems or delayed return of protective reflexes, especially in older or high-risk patients. For outpatient procedures, quicker recovery can lead to earlier discharge and better patient flow. Overall, shorter recovery times help improve workflow, reduce the need for extended monitoring, lower sedation-related risks, and allow patients to return to normal activities sooner, all of which contribute to better healthcare efficiency and patient satisfaction.

Few studies have investigated the management of sedation using continuous remimazolam infusion in non-intubated patients. By achieving BIS values within the target range of 60 to 80, we found that the median continuous dose of remimazolam of 0.19 (0.1) mg/kg/h provided precision in tailoring sedation to the desired needs. The goal of supplementing BIS with MOAA/S and RASS as parameters of depth of sedation was to address the limitations of BIS alone, enable more precise drug titration, better intraoperative sedation assessment, and enhance complications prediction. A study that targeted RASS score of -2 to 0 to titrate remimazolam dosing for continuous sedation to relief agitated delirium in non-intubated older patients after orthopedic surgery found that the maintenance dose required to achieve it was 0.1-0.3 mg/kg/h, results similar to our study.[22] In elderly patients undergoing hip replacement under combined spinal-epidural anesthesia, to maintain BIS values <80 and MOAA/S score around 3, the ED50 and ED95 for continuous remimazolam infusion were found to be 0.212 mg/kg/h and 0.288 mg/kg/h respectively, also consistent with our findings.[23]

A continuous propofol infusion of 1.91 (1.0) mg/kg/h was used to maintain BIS level between 60 and 80. Many studies have shown that 2.5 – 3 mg/kg/h of continuous propofol infusion is sufficient to achieve the target BIS values of 60-80 for sedation.[18,19] The patients in our study were not healthy (ASA II and III) with a mean age over 65 years. Studies indicate that advanced age and higher ASA classification reduce propofol requirements, which is consistent with our findings.[24–26]

The only statistically significant difference in adverse effects observed was related to memory of the procedure. Only 10.0% of patients in the remimazolam group reported experiencing memory of the procedure, compared to 40.0% in the propofol group (p=0.017). In a previous studies, using larger dosing regimen, 96.6% of patients reported no or minimal memory of the procedure.[13] Other findings regarding memory recovery are mostly from studies following general anesthesia, with remimazolam groups having poorer memory recovery.[27] A recent systematic review and meta-analysis comparing remimazolam and propofol for procedural sedation found statistically significantly lower incidence of hypotension with remimazolam.[28] In contrast, our results show no statistically significant difference in hypotension between the groups, though hypotension occur more frequent in the remimazolam group (20.0% vs. 10.0%, respectively). This may be attributed to the use of spinal anesthesia, and lower propofol dose in our study. Hypoxia is another side-effect that is occurring more frequently with propofol than with remimazolam.[29] In our study, we documented hypoxia in 10.0 % cases of

the remimazolam group and 23.3% in the propofol group. Although not statistically significant, it correlates with previous findings.[30,31] The incidence of apnea was very low, occurring in only 1 case in both groups and resolved without the need for intervention. However, recent study has found a notable incidence of apnea during moderate to deep remimazolam sedation, using 0.1 mg/kg in 2 minutes followed by 0.5 mg/kg/hr of remimazolam. While the doses were higher than those used in our study, they highlight the need for close monitoring despite the absence of severe adverse events.[32] Although in this study no significant side effects were recorded, nor did they lead to discontinuation of medication or surgery, an important possibility is the use of flumazenil as an antagonist to remimazolam. A notable limitation associated with propofol is its absence of a specific antagonist, thereby conferring an advantage to remimazolam.

This study is limited by its relatively small sample size, which may affect result interpretation, and by the clinical relevance of a 3-minute difference in recovery time between the drugs. As a single-center study involving sedation only in patients undergoing spinal anesthesia, the generalizability of these findings to other clinical settings or patient populations is limited. However, these findings support further investigation of remimazolam as a valuable sedative, especially for procedures requiring precise sedation control. Current studies show significant variability in dosing regimens, patient demographics, severity, and endpoints, highlighting the need for further research to establish more informative protocols or best practice standards.

Conclusion

Our findings have shown that continuous infusion of remimazolam exhibits non-inferior efficacy and safety in providing sedative and hypnotic effects for intraoperative sedation in non-healthy subjects undergoing spinal anesthesia, compared to propofol. Remimazolam has shown faster onset, significantly better recovery time and amnestic profile.

Disclosure

The authors declare no conflicts of interest. No funding was received for this study.

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