European Journal of Medical Research

RESEARCH

Open Access

Comparison of effect of remimazolam and propofol on respiration of patients under deep sedation for colonoscopy: a prospective multicenter randomized controlled trial

Zhengjia Wang[1†], Renshu Zhan[1†], Liqun Mo[1,9], Jin Zhang[2], Jie Hu[3], Shoupeng Tan[4], Qiongzhen He[5], Ping Li[6], Wekong Sun[7], Xiaobin Wang[1,9], Jun Jiang[8], Li Liu[1,9], Yingying Zhang[1,9] and Yiping Bai[1,9*]

Abstract

Background Remimazolam recently became available as a sedative. The comparison of the respiratory suppression effects of remimazolam and propofol under deep sedation for colonoscopy was not thoroughly unclear, particularly with regard to the novel metric of time to first airway intervention. The goal of this study was to systemically compare the respiration profiles of the patients sedated with remimazolam and propofol at the comparable sedation level in the patients undergoing colonoscopy.

Methods Four hundred-fifty outpatients were randomly assigned to remimazolam (Group Rem, $n=225$) and propofol (Group Pro, $n=225$). The target sedation level was the modified Observer's Assessment of Alertness/Sedation ≤ 2. The primary outcome was elapsed time from anesthesia induction to first airway intervention. Secondary outcomes included incidence and severity of hypoxia and apnea, minute ventilation (MV), tidal volume (TV), and respiratory rate (RR).

Results The elapsed time from induction to the first airway intervention was 11 ± 8 min in Group Rem (n = 208) vs. 5 ± 6 min in Group Pro ($n=208$, $P<0.001$). Patients in Group Rem required less frequent airway intervention and had a lower incidence of and shorter duration of apnea than patients in Group Pro (all $P<0.001$). MV at 1 min, 2 min, 4 min post-induction, and at the end of the procedure were higher in Group Rem than those in Group Pro ($P<0.001$).

Conclusions Patients sedated with remimazolam vs. propofol during colonoscopy maintain improved respiration and require less frequent airway intervention, and have lower incidence of adverse events.

Clinical trial registration and registry URL ChiCTR2000034527, registered at www.chictr.org.cn

Keywords Remimazolam, Ventilation, Colonoscopy, Sedation, Anesthesia

†Zhengjia Wang and Renshu Zhan have contributed equally to share first authorship.

*Correspondence:
Yiping Bai
baiyiping0608@163.com
Full list of author information is available at the end of the article

Colorectal cancer screening guidelines universally endorse colonoscopy initiation at ≥ 45 years, with procedural sedation being integral to patient compliance and diagnostic accuracy [1, 2]. While propofol remains predominant for its rapid onset/offset and antiemetic properties, its dose-dependent cardiopulmonary depression and lipid-associated complications pose significant limitations [3, 4]. Midazolam offers better hemodynamic stability and reversibility but suffers from prolonged recovery and delirium risks [5–8]. The recent introduction of remimazolam presents a novel benzodiazepine derivative combining midazolam's safety profile with propofol-like pharmacodynamics, featuring ultra-short context-sensitive half-life (8–15 min) and organ-independent metabolism [9–11].

Although moderate sedation remains standard, deep sedation allows for better procedural tolerance and patient satisfaction, which is crucial for the success of colonoscopy. Current evidence predominantly evaluates remimazolam in moderate sedation contexts, leaving critical knowledge gaps regarding its respiratory safety profile during deep sedation compared to propofol [8, 9]. This distinction is clinically paramount as deep sedation intrinsically elevates respiratory depression risks while optimizing endoscopic conditions. The balance between enhanced procedural efficacy and respiratory safety constitutes a pivotal consideration in sedation protocol optimization.

Our multicenter randomized controlled trial specifically investigates respiratory effects of these agents under standardized deep sedation during colonoscopy. We hypothesize that remimazolam induces less respiratory suppression than propofol at equivalent sedation depths, potentially offering a safer pharmacological profile for prolonged endoscopic procedures. By employing continuous capnography and standardized opioid co-administration, this study aims to provide evidence-based guidance for sedation regimen selection in gastrointestinal endoscopy suites.

Methods

This prospective, multicenter, randomized, single-blind study was approved by the Institutional Review Board of Affiliated Hospital of Southwest Medical University (KY2020090), and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at www.chictr.org.cn (ChiCTR2000034527, Principal investigator: Yiping Bai, Date of registration: July 8, 2020). Secondary approval was obtained from all local Institutional Review Boards. The study was conducted following the original protocol in the endoscopy suite at each institution between August 1, 2020, and June 1, 2021.

Four hundred-fifty subjects scheduled for an elective colonoscopy under deep sedation were enrolled from the gastrointestinal endoscopy center. Inclusion criteria was as following: (1) 18 years or older scheduled for colonoscopy under deep sedation; (2) American Society of Anesthesiology classification of I–III; (3) able to breath through nose and mouth. The exclusion criteria included: (1) allergic to benzodiazepines or propofol; (2) pregnancy; (3) participated in clinical trials of other drugs in the past 3 months; (4) patients with ASA class ≥ IV, severe obesity (BMI ≥ 35 kg/m^2), or uncontrolled cardiopulmonary conditions; (5) patients refusal. And anticipated general anesthesia with endotracheal tube or supraglottic airway insertion.

First airway intervention was defined as time from initiation of propofol/remimazolam bolus and/or infusion to the first airway intervention. Hypoxia was defined as SpO_2 < 90%. Hypopnea was defined as tidal volume decreased more than 50% of the baseline value. Apnea was defined as no spontaneous breathing longer than 10 s.

Study procedure

The anesthesia providers included an attending anesthesiologist and certified registered nurse anesthetists (CRNAs). Brief instructions on the evaluation of ventilation were provided to the care team prior to the procedure.

A web-based computerized and central randomization service was used for the allocation of the participants (http://www.randomizer.at). Centralized randomization (1:1) is performed by the Affiliated Hospital of Southwest Medical University. Concealment of random allocation was ensured by the computerized and central randomization service. After obtaining written informed consent, patients were randomized to Group Rem (induction and maintenance of deep sedation with remimazolam) or Group Pro (induction and maintenance of deep sedation with propofol).

All patients were placed in the left lateral position before anesthesia induction.

Standard monitors were applied including electrocardiography (ECG), non-invasive blood pressure (NIBP), and SpO_2. Oxygen supplementation was done via face mask at a flow rate of 6 l/minute. Patients adapted to the face mask for 3–5 min, and sedatives were given. Minute ventilation (MV), tidal volume (TV), and respiratory rate (RR) were continuously recorded with an anesthesia machine (Carestation 620, Ge Medical Systems Co., Ltd., China), from this point until the end of the procedure. The providers were advised to intervene at any time to handle hypoxia and/or apnea of the patients in each group based on their own clinical judgments. Given

that the same anesthesia provider was responsible for both groups and the sample size was sufficiently large, the comparability between the two groups is ensured. Meanwhile, for patient safety, airway interventions were mandatory and were performed based on clinical signs of respiratory compromise, which included: (1) oxygen saturation (SpO_2) < 90%, (2) apnea lasting more than 10 s, (3) significant respiratory effort reduction.

The dosage of sedatives was determined based on the target sedation level (MOAA/S ≤ 2) and adjusted according to the patient's response. The initial doses and maintenance infusion rates were set according to the study protocol, and additional doses were given as needed to maintain the target sedation level. The dosage adjustments were made by the anesthesia providers based on clinical judgment and the patient's vital signs.

Patients in both groups, received sufentanil 5 μg before induction. Then patients in Group Pro received propofol continuous pump infusion at a rate of 2 mg/kg/min for 1 min, followed by a rate of 4 mg/kg/h to maintain until completion of the procedure. In Group Rem, patients received remimazolam infusion at a rate of 0.2 mg/kg/min for 1 min, and then 1.5 mg/kg/h until the completion of the procedure. The modified Observer's Assessment of Alertness/Sedation (MOAA/S) was evaluated every 10 s after the induction dose. To ensure the reproducibility of sedation level assessment, the anesthesia providers were trained in a standardized manner before the study. They were required to use a unified assessment standard: when evaluating MOAA/S, they should observe the patient's response to voice commands, tactile stimulation in sequence. Specifically, first, call the patient's name loudly. If the patient responds immediately, the score is 5; if the patient responds sluggishly, the score is 4; if the patient only responds to repeated or loud voice commands, the score is 3; if the patient responds only to tactile stimulation, the score is 2; if the patient does not respond to tactile stimulation, the score is 1. Only when the MOAA/S score reached ≤ 2 for two consecutive evaluations at 10-s intervals was the colonoscopy procedure started. If it was not sufficient to maintain appropriate sedation 1 min after the initial dose, up to a maximum of five supplemental doses were given to patients (remimazolam 0.05 mg/kg or propofol 0.5 mg/kg for each time). If the initial dose and the supplemental doses were insufficient to obtain adequate sedation for the procedure in the Group Rem, sedative rescue medication (propofol) was to be administered at the start of the procedure at the anesthesia provider's discretion. Ephedrine 10–20 mg IV was to be given to prevent hypotension, and atropine 0.3–0.5 mg IV was given to prevent bradycardia. Anesthesia providers were allowed to treat hypoxia and/or apnea based on their clinical judgments, and used any airway interventions they normally use, including performing chin lift or jaw thrust, inserting nasal or oral airways, manually assisted ventilation, placing laryngeal mask airway (LMA) or tracheal tube.

The primary outcome was the elapsed time from anesthesia induction to first airway intervention. The secondary outcomes included incidence and severity of hypoxia and apnea, minute ventilation (MV), tidal volume (TV), and respiratory rate (RR). Adverse events included tachycardia, bradycardia, hypotension, hypotension, injection pain, hiccup, nausea/vomiting, delayed recovery.

Statistical analysis

We chose elapsed time from anesthesia induction to first airway intervention as the primary outcome. Based on a previous study [12], it was roughly 5 min in the Group Pro, and the increase in elapsed time from anesthesia induction to first airway intervention in the Group Rem would be 20% to 6 min, with SD ± 2 min. The sample size of 152 and 76 patients on each arm should allow us to detect the difference between the two groups with a power of 0.8 and a type I error rate of 5%. We rounded to 160 patients, allowing a drop rate of approximately 10%.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) 20.0 (IBM). The normal distribution of data was assessed using Kolmogorov–Smirnov normality tests. The variability of the data was measured by Levene's test. Unless otherwise noted, data are presented as the mean (SD) or percentage (%). Unpaired two-tailed *t*-test, ANOVA, and Chi-square test were used to compare quantitative and categorical outcomes. Significance was defined as a two-sided *P*-value < 0.05.

Results

A total of 450 subjects were enrolled and randomized into the Group Rem or Group Pro. 34 patients were excluded, with detailed information described in Fig. 1, leaving 416 subjects for the final analysis. There were no differences between the two groups in demographic characteristics, procedure length, and dose of anesthetics and analgesics (Table 1).

Elapsed time from anesthesia induction to first airway intervention was 11 ± 8 min in the Group Rem and 5 ± 6 min in the Group Pro ($P < 0.001$), fewer patients in the Group Rem received airway interventions, 46/208 (22%) vs. 128/208 (62%) in the Group Pro ($P < 0.001$). Subgroup analysis of airway interventions showed that chin lift occurred in 83% (38/46) of cases in the Group Rem vs. 47% (60/128) in the Group Pro ($P < 0.001$), Jaw thrust occurred more frequently in the Group Pro (54%, 69/128) compared to the Group Rem (20%, 9/46) ($P < 0.001$), 21% (27/128) of cases in the Group Pro needed manual assisted ventilation with no one in the Group Rem

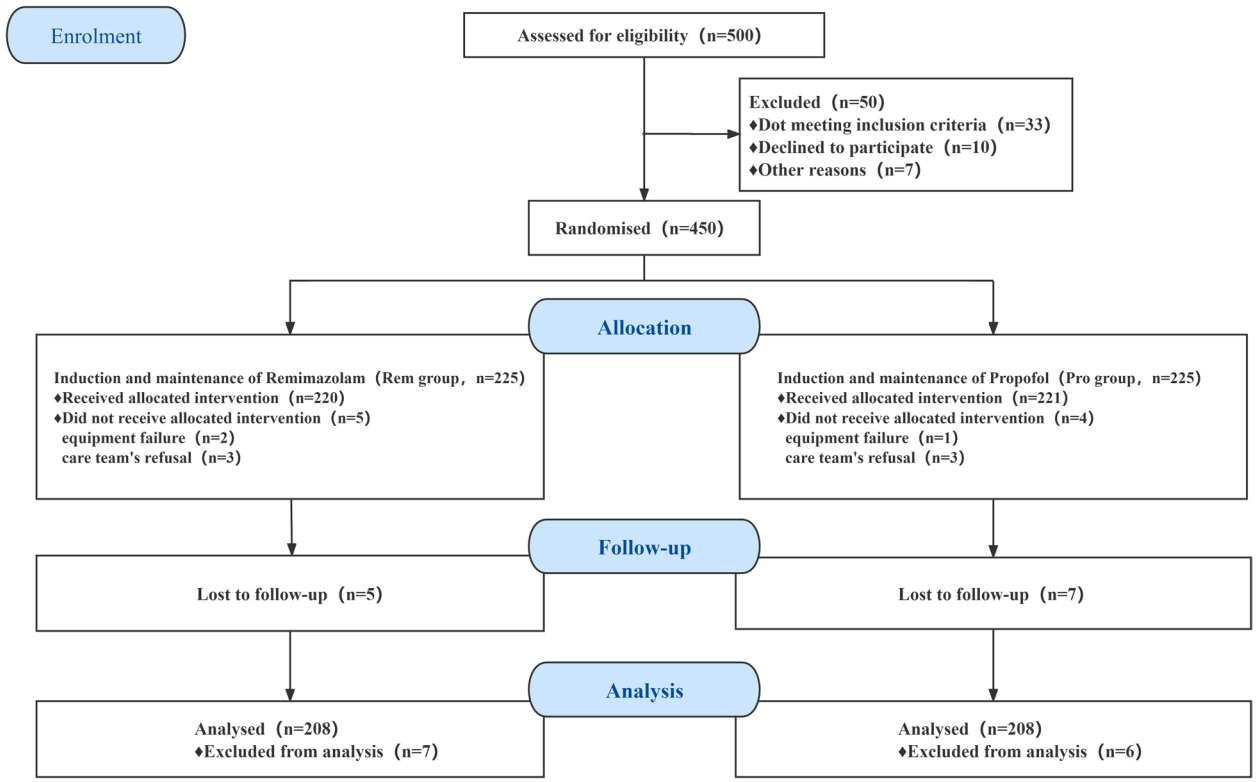

Fig. 1 Subjects enrollment and randomization**.** Patients in the Group Rem received remimazolam for deep sedation, and in the Group Pro, patients were given propofol

($P=0.001$). No patient in either group required oral or nasal airway insertion, laryngeal mask airway placement, or tracheal intubation.

The respiratory variables between Group Rem and Pro were as following. Average number of apneic episodes (0.25 ± 0.51 vs. 1.22 ± 1.73, $P<0.001$), total duration of apnea (7.64 ± 15.25 s vs. 55.53 ± 103.76 s, $P<0.001$), total duration of apnea/procedure length ($1.38 \pm 3.24\%$ vs. $7.24 \pm 13.93\%$, $P<0.001$) were significantly less in the Group Rem compared to Group Pro (Table 2).

MV and RR at 1 min (both $P<0.001$), 2 min (both $P<0.001$), 4 min (both $P<0.001$) post-induction, and at the end of the procedure (both $P<0.001$) were significantly lower in the Group Pro compared to the Group Rem. TV at 1 min ($P<0.001$), 2 min ($P<0.001$), 4 min ($P<0.001$) post-induction were lower in the Group Pro compared to the Group Rem. After standardizing the data, the ratio of $MV_{1,2,4,6\ min\ Post\text{-}Induction}/MV_{Baseline}$, $MV_{Procedure\text{-}End}/MV_{Baseline}$, $RR_{1,2,4,6\ min\ Post\text{-}Induction}/RR_{Baseline}$, $RR_{Procedure\text{-}End}/RR_{Baseline}$, and $TV_{1,2,4\ min\ Post\text{-}Induction}/TV_{Baseline}$ were significantly lower in the Group Pro compared to the Group Rem (all $P<0.001$, Fig. 2).

The first success rate in the Group Rem was 75.96% vs. 85.58% in the Group Pro ($P=0.013$), with no difference in the procedure success rate (96.75% vs. 100%, $P=0.061$). Adverse events (AEs) were reported in 14.90% (31/208) patients in the Group Rem vs. 63.46% (132/208) patients in the Group Pro ($P<0.001$), including a lower incidence of bradycardia, hypotension, hypotension needs treatment, injection pain (all $P<0.05$). A hiccup occurred more frequently in the Group Rem than in the Group Pro ($P<0.001$). Time to full alert in the Group Rem was longer than in the Group Pro ($P<0.001$), with no difference in delayed recovery between the two groups ($P=0.248$) (Table 3).

Discussion

In spontaneously breathing patients under deep sedation during colonoscopy, remimazolam, compared with propofol, (1) reduces the need for airway intervention and the possibility of hypoxia; (2) provides improved respiration; (3) reduces the incidence of adverse events.

Despite sharing GABAa receptor activity with propofol, remimazolam's clinical profile in procedural sedation remained incompletely characterized [6, 7]. Our study demonstrated that at comparable sedation levels during colonoscopy, remimazolam achieved similar procedural conditions while providing superior respiratory safety and fewer adverse events compared to propofol.

Table 1 Demographics and characteristics of the two study arms

Characteristics	Rem group ($n=208$)	Pro group ($n=208$)
Sex (male/female)	110/98	111/97
ASA physical status		
I	97	100
II	105	103
III	6	5
Age (year)	52 ± 12	51 ± 13
Height (cm)	162 ± 8	162 ± 8
Weight (kg)	60 ± 10	60 ± 10
BMI (kg/m^2)	23 ± 3	23 ± 3
Hear rate (bites/min)	77 ± 12	77 ± 13
Systolic pressure (mm Hg)	135 ± 19	139 ± 21
Diastolic pressure (mm Hg)	81 ± 12	81 ± 10
Respiratory rate (times/min)	17 ± 3	17 ± 4
Previous history		
Anxious	31	29
Alcoholism	33	37
Hypertension	62	55
Diabetes	13	19
COPD	0	0
Drug history	0	0
Routine diagnosis		
Colonic polyp	79	82
Crohn's disease	12	11
Others	12	15
Intravenous anesthetics and analgesics		
Sufentanil (iv, μg)	5	5
Procedure length (min)	13 ± 8	13 ± 6

Values were expressed as the mean ± SD or absolute number. Patients in Rem group received remimazolam for deep sedation. Patients in Pro group received propofol for deep sedation

Our primary outcome—time from anesthesia induction to first airway intervention—revealed significant differences between the medications. Remimazolam extended this interval to 11 min compared to 5 min with propofol. While a 6-min difference might appear modest for individual cases, its clinical significance becomes apparent in contemporary practice settings where anesthesiologists frequently manage multiple sedated patients simultaneously [13, 14]. This extended intervention-free window has particular relevance for high-risk patients (ASA III or above, elderly, or obese) and in settings with high procedural volumes [15–17]. For high-risk patients, this additional time allows for more careful monitoring of respiratory parameters before the need for airway intervention. It provides an opportunity to detect early signs of respiratory compromise and take preventive measures, reducing the risk of severe respiratory events. In high-volume endoscopic centers, where the throughput of patients is high, the longer time before airway intervention means that anesthesiologists can manage patients more efficiently. They can allocate their time and resources better, attending to other patients while still ensuring the safety of those sedated with remimazolam. Even with nurse anesthetist supervision, this additional buffer time enhances patient safety and reduces management complexity, as it provides more time for careful monitoring and timely intervention when needed.

While no hypoxic events occurred in either group due to prompt interventions, the need for airway intervention differed significantly (22% with remimazolam vs. 62% with propofol), suggesting remimazolam's superior respiratory safety profile. This zero incidence of hypoxia contrasts with previous studies reporting SpO_2 below 90% in up to 22% of patients [12]. Our improved safety outcomes can be attributed to three key factors: careful patient selection excluding those with obesity or serious cardiopulmonary diseases, standardized pre-oxygenation protocols (6 L/min for > 2 min), and proactive airway intervention before any significant oxygen desaturation.

However, we found MV decreased in both groups after deep sedation, with more decrease in propofol group. Another interesting findings were that remimazolam almost did not inhibit the RR of patients, with obvious inhibition of RR in the propofol group. According to $MV = TV \times RR$, the decrease in MV was mainly caused by the TV decrease using remimazolam, the inhibition of propofol on patients' respiration was manifested in the reduction of TV and RR. It can also be inferred that propofol has a more significant inhibition on RR than remimazolam from the increase in the average number of apneic episodes and total duration of apnea. A key finding was the differential effects on respiratory parameters: remimazolam primarily affected tidal volume while preserving respiratory rate, whereas propofol suppressed both. These distinct respiratory patterns suggest different mechanisms of action, which may have implications for patients requiring spontaneous breathing during difficult intubation procedures.

Another interesting finding is that airway interventions were easier in the Group Rem than in the Group Pro. We know that chin lift and jaw thrust are easier than manually assisted ventilation, chin lift are easier than jaw thrust, supraglottic airway device and endotracheal intubation need more preparation. No patients received the supraglottic airway device or endotracheal intubation in both groups. All patients needed only chin lift and jaw

Table 2 Incidence and duration of airway intervention, oxygen desaturation, apnea and hypopnea

	Rem group ($n=208$)	Pro group ($n=208$)	*P*
Elapsed time from anesthesia induction to first airway intervention (min)	11 ± 8	5 ± 6	< 0.001
Airway intervention	46/208 (22%)	128/208 (62%)	< 0.001
Chin lift	38/46 (83%)	60/128 (47%)	< 0.001
Jaw thrust	9/46 (20%)	69/128 (54%)	< 0.001
Manual assisted ventilation	0/46 (0%)	27/128 (21%)	0.001
Oral or nasal airway placement	0/46 (0%)	0/128 (0%)	NA
laryngeal mask airway placement or tracheal intubation	0/46 (0%)	0/128 (0%)	NA
Interrupt colonoscopy	0/46 (0%)	0/128 (0%)	NA
Minimum oxygen saturation			
90–100%	208/208 (100%)	208/208 (100%)	NA
95–100%	208/208 (100%)	208/208 (100%)	NA
90–95%	0/208 (0%)	0/208 (0%)	NA
< 90%	0/208 (0%)	0/208 (0%)	NA
Average number of apneic episodes	0.25 ± 0.51	1.22 ± 1.73	< 0.001
Median number of apneic episodes (25%-75%)	0 (0–0)	1 (0–1)	< 0.001
Total duration of apnea (sec)	7.64 ± 15.25	55.53 ± 103.76	< 0.001
Total duration of apnea/procedure length (%)	1.38 ± 3.24	7.24 ± 13.93	< 0.001

Values were expressed as the mean ± SD, absolute number (percentage), unless otherwise specified. Elapsed time from anesthesia induction to first airway intervention was defined as time from initiation of propofol/remimazolam bolus and/or infusion to the first airway intervention. If no intervention was provided, the elapsed time was recorded as procedure time. Manual assisted ventilation is a case where tidal volume is less than 50 ml after induction and ventilation cannot be improved by chin lift and jaw thrust. Minimum oxygen saturation is defined as the lowest recorded SpO_2 value during the procedure, reflecting the most severe level of oxygen desaturation experienced by the patient. Apnea was defined as no spontaneous breathing longer than 10 s

thrust to improve respiration in the remimazolam group, but 21% of patients needed manually assisted ventilation in the propofol group. Furthermore, a chin lift could improve spontaneous ventilation in 83% of patients in the remimazolam group vs. 47% in the propofol group. More patients (54% vs. 20%) needed jaw thrust to open the upper airway in the propofol group. We know that both sedatives meet the need for colonoscopy procedures. However, the easier the airway intervention, the greater the significance of clinical promotion, especially in the medical situations of fewer anesthetists and more endoscopic patients.

We also found that patients sedated with remimazolam recovered slower than propofol. The time to full alert using remimazolam was 9.14 min vs. 6.83 min using propofol. The slower recovery of remimazolam was through the following principles. First, the clearance rate of remimazolam in vivo (0.88–1.37 l/min) was slower than that of propofol (1.5–2 l/min). Secondly, the onset time of remimazolam is 1–3 min, and the full awake time is 8–40 min, which is slower than that of propofol [18]. Third, patients in the remimazolam group received more rescue sedatives than the propofol group (23.08% vs. 14.42%), which prolonged the sedation time. Clinically, the slower recovery of remimazolam may affect the patient's turnover rate in the post-anesthesia care unit. However, remimazolam has a specific reversal agent, flumazenil, which makes its sedative effect more controllable. We found that MOAA/S increased to 5 points in 1 min after intravenous injection of flumazenil 0.2 mg in the 3 delayed recovery patients, without re-sedation or discomfort. Studies have shown that remimazolam's sedative effect can be reliably reversed by flumazenil with minimal risk of re-sedation, as both agents have similar elimination half-times (approximately 48 min). [5–7].

Six patients in the remimazolam group experienced hiccups, while no hiccup-related adverse reactions were observed in the propofol group. Hiccups during colonoscopy may be triggered by the stimulation of the phrenic nerve during the colonoscopy procedure. This result is consistent with the reported adverse reactions of remimazolam during gastroscopy and colonoscopy [19, 20]. Since no patient in the propofol group had hiccups, it cannot be ruled out that it is related to the remimazolam drug itself. However, there is currently no research explaining the pharmacological mechanism by which remimazolam causes hiccups. This phenomenon can be further explored in subsequent studies.

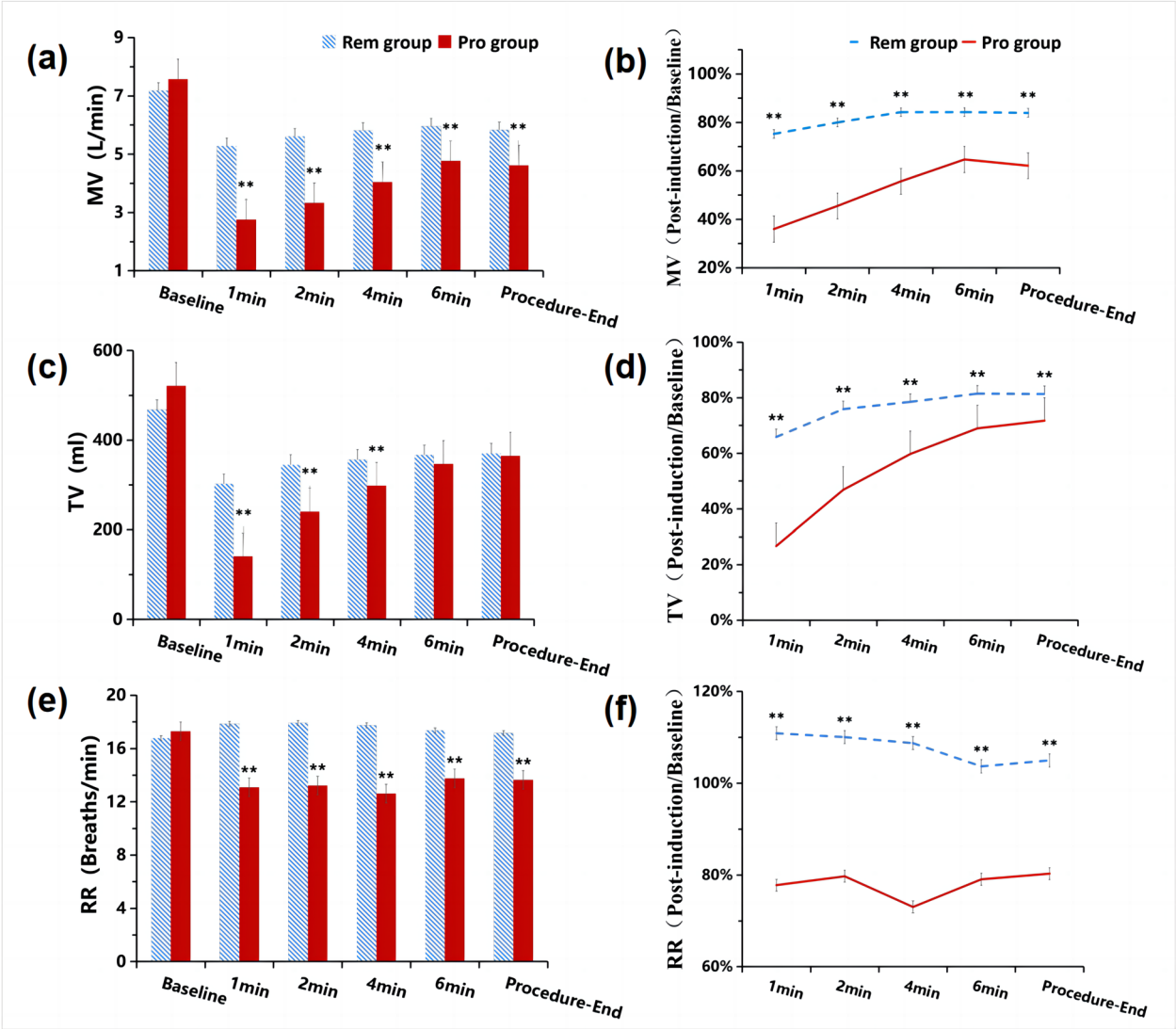

Fig. 2 Respiratory measurements at six-time points. Min ventilation (MV, a), tidal volume (TV, c), and respiratory rate (RR, e) were recorded at the time points before anesthesia induction (baseline), 1, 2, 4, and 6 min after induction, and at the end of the procedure. Post-induction/baseline was the ratio of six time points to baseline values. Values were expressed as the mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.001$

There are several potential limitations to this study. First, No BIS. But sedation level was determined with clinical assessment, and this study was randomized and the sample size was large. We assume that the difference in the sedation levels between the two arms is NS and does not affect our conclusion. Second, No blind. The sedatives could not be blinded to the clinician or research staff, considering the safety of the patients. However, all parameters analyzed were automatically recorded except for the elapsed time from induction first airway intervention and the number and length of airway interventions. Third, sedation level at initiation of procedure was not protocolized. The gastroenterologists might start procedure before the target sedation level was achieved, but the occurrence was few. We assume that it does not affect our conclusion. Fourth, our study population predominantly comprised non-obese patients (median BMI: 24.1 kg/m^2) without high-risk comorbidities. Given that obesity and systemic disease may alter drug pharmacokinetics and sedation-related respiratory responses, our findings may not fully generalize to these subgroups. Future studies targeting these populations are warranted to validate the broader applicability of remimazolam in diverse clinical settings.

Table 3 Efficacy and safety data

	Rem group ($n=208$)	Pro group ($n=208$)	*P*
Procedure success rate	96.75% (203/208)	100% (208/208)	0.061
First success rate	75.96% (158/208)	85.58% (178/208)	0.013
Times of rescue sedation in 15 min			
< 3 times	23.56% (46/208)	12.50% (26/208)	0.010
≥ 3 times	1.92% (4/208)	1.92% (4/208)	1.000
Time to full alert (min)	9.14 ± 5.29	6.83 ± 2.36	0.000
Adverse events (AEs) rates	14.90% (31/208)	63.46% (132/208)	0.000
Tachycardia	1.44% (3/208)	0.48% (1/208)	0.623
Bradycardia	0.48% (1/208)	4.33% (9/208)	0.010
Hypotension	2.40% (5/208)	21.15% (44/208)	0.000
Hypotension needs treatment	0.48% (1/208)	13.94% (29/208)	0.000
Injection pain	0	28.37% (59/208)	0.000
Hiccup	6.73% (14/208)	0	0.000
Nausea/vomiting	0	0	NA
Delayed recovery	1. (3/208)	0	0.248
Others	0	0	NA

Values were expressed as absolute number (percentage). The procedure success was defined as completion of the procedure without requirement for rescue sedative medication, and without requirement for more than 5 top-ups of propofol or remimazolam within any 15-min period post-induction. First success rate was defined as the initial dose was sufficient to obtain adequate sedation for the procedure. Time to full alert was defined as the time from the end of medication to the first of 3 consecutive MOAA/S score of 5. Tachycardia was defined as heart rate > 100 beats/min. Bradycardia was defined as heart rate < 50 beats/min. Hypotension was defined as 30% reduction in mean arterial pressure from the basic value, or systolic blood pressure < 90 mm Hg. Hypotension requiring treatment was defined as blood pressure of hypotension is reduced to 50% of the basic value, or the systolic blood pressure is less than 80 mm Hg. Injection pain was defined as the patient's complaint that there was obvious pain at the injection site during intravenous medication. Delayed recovery was defined as failure to achieve an MOAA/S score ≥ 4 (response to name spoken in normal tone) within 20 min after drug discontinuation. Modified Observer´s Assessment of Alertness/Sedation (MOAA/S) score, grade 5: fully awake, with normal response to name calling; grade 4: slow to respond to name calls; grade 3: only respond to loud or/and repeated calls; grade 2: respond to nudge/patting; grade 1: no response to nudge/patting; grade 0: no response to pinching earlobe

Conclusion

Patients sedated with remimazolam vs. propofol during colonoscopy maintain improved respiration and require less frequent airway intervention, and have lower incidence of adverse events.

Acknowledgements
The authors have no conflicting interests with any companies.

Prior presentations
No presentation of work at conference meetings.

Author contributions
Zhengjia Wang, M.D.: Study design, Institutional Review Board application, patient enrollment, data collection, data analysis, manuscript preparation. Renshu Zhan, M.D.: Study design, Institutional Review Board application, patient enrollment, data collection, data analysis, manuscript preparation. Liqun Mo, M.D.: Patient enrollment and manuscript preparation. Jin Zhang, M.D., Ph.D.: Institutional Review Board application and manuscript preparation. Jie Hu, M.D., Shoupeng Tan, M.D., Qiongzhen He, M.D., Ping Li, M.D., Wekong Sun, M.D.: Data collection. Xiaobin Wang, M.D.: Study design, Institutional Review Board application, data collection, data analysis, and manuscript preparation. Jun Jiang, M.D., Ph.D.: Study design, Institutional Review Board application, data collection, data analysis, and manuscript preparation. Li Liu, M.D.: Study design, Institutional Review Board application, data collection, data analysis, and manuscript preparation. Yingying Zhang, M.D., Ph.D.: Study design, Institutional Review Board application, data analysis, and manuscript preparation. Yiping Bai, M.D., Ph.D.: Study design, Institutional Review Board application, data analysis, and manuscript preparation.

Funding
The study was supported by the Sichuan International Medical Exchange & Promotion Association (HR21002), and Sichuan Science and Technology Program (2022YFS0632, 2022YFS0627).

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

Declarations

Ethical approval and consent to participate
This prospective, multicenter, randomized, single-blind study was approved by the Institutional Review Board of Affiliated Hospital of Southwest Medical University (KY2020090), and written informed consent was obtained from all subjects participating in the trial.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, The Affiliated Hospital, Southwest Medical University, 25 Taiping Street, Luzhou 646000, China. [2]Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, USA. [3]Department of Anesthesiology, Xuyong County People's Hospital, Xuyong, China. [4]Department of Anesthesiology, The Second People's Hospital of Guangyuan, Guangyuan, China. [5]Department of Anesthesiology, Guangyuan Mental Health Center, Guangyuan, China. [6]Department of Anesthesiology, The People's Hospital of Yuechi, Yuechi, China. [7]Department of Anesthesiology, Cangxi People's Hospital, Cangxi, China. [8]Department of General Surgery (Thyroid Surgery), The Affiliated Hospital of Southwest Medical University, Luzhou,

China. [9]Anesthesiology and Critical Care Medicine Key Laboratory of Luzhou, Luzhou, China.

Received: 20 November 2023 Accepted: 26 March 2025
Published online: 07 April 2025

References

1. Keswani RN, Crockett SD, Calderwood AH. AGA clinical practice update on strategies to improve quality of screening and surveillance colonoscopy: expert review. Gastroenterology. 2021;161(2):701–11.
2. Yang YL, Li SS, Wang XB, Li JN. Painless colonoscopy: a pilot study of a 5.9-mm endoscope for routine colonoscopy. Chin Med J. 2018;131(7):857–8.
3. Steenholdt C, Jensen JT, Brynskov J, Møller AM, Limschou AC, Konge L, Vilmann P. Patient satisfaction of propofol versus midazolam and fentanyl sedation during colonoscopy in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2022;20(3):559-568.e555.
4. Walsh CT. Propofol: milk of amnesia. Cell. 2018;175(1):10–3.
5. Rex DK, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, Barish CF, Pruitt R, Cash BD, Quirk D, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. Gastrointest Endosc. 2018;88(3):427-437.e426.
6. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. Front Pharmacol. 2021;12:690875.
7. Lee A, Shirley M. Remimazolam: a review in procedural sedation. Drugs. 2021;81(10):1193–201.
8. Io T, Saunders R, Pesic M, Petersen KU, Stoehr T. A miniature pig model of pharmacological tolerance to long-term sedation with the intravenous benzodiazepines; midazolam and remimazolam. Eur J Pharmacol. 2021;896:173886.
9. Sneyd JR, Absalom AR, Barends CRM, Jones JB. Hypotension during propofol sedation for colonoscopy: a retrospective exploratory analysis and meta-analysis. Br J Anaesth. 2022;128(4):610–22.
10. Antkowiak B, Rammes G. GABA(A) receptor-targeted drug development -New perspectives in perioperative anesthesia. Expert Opin Drug Discov. 2019;14(7):683–99.
11. Keam SJ. Remimazolam: first approval. Drugs. 2020;80(6):625–33.
12. Bai Y, Xu Z, Chandrashekar M, St Jacques PJ, Liang Y, Jiang Y, Kla K. Comparison of a simplified nasal continuous positive airways pressure device with nasal cannula in obese patients undergoing colonoscopy during deep sedation: a randomised clinical trial. Eur J Anaesthesiol. 2019;36(9):633–40.
13. Krigel A, Chen L, Wright JD, Lebwohl B. Substantial increase in anesthesia assistance for outpatient colonoscopy and associated cost nationwide. Clin Gastroenterol Hepatol. 2019;17(12):2489–96.
14. Gururatsakul M, Lee R, Ponnuswamy SK, Gilhotra R, McGowan C, Whittaker D, Ombiga J, Boyd P. Prospective audit of the safety of endoscopist-directed nurse-administered propofol sedation in an Australian referral hospital. J Gastroenterol Hepatol. 2021;36(2):490–7.
15. Hedenstierna G, Tokics L, Scaramuzzo G, Rothen HU, Edmark L, Öhrvik J. Oxygenation impairment during anesthesia: influence of age and body weight. Anesthesiology. 2019;131(1):46–57.
16. Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, Wahidi M, Shojaee S, Tanner NT, Callahan SP, et al. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest. 2019;155(1):137–46.
17. Makarem J, Larijani AH, Eslami B, Jafarzadeh A, Karvandian K, Mireskandari SM. Risk factors of inadequate emergence following general anesthesia with an emphasis on patients with substance dependence history. Korean J Anesthesiol. 2020;73(4):302–10.
18. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: Part I pharmacokinetics and clinical pharmacodynamics. Anesthesiology. 2020;132(4):636–51.
19. Chen S, Wang J, Xu X, et al. The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: a multicentered, randomized, positive-controlled, phase III clinical trial. Am J Transl Res. 2020;12(8):4594–603.
20. Chen SH, Yuan TM, Zhang J, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, phase III trial. J Gastroenterol Hepatol. 2021;36(2):474–81.

Publisher's Note