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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Remimazolam tosilate infusion has a lower incidence of hypotension than propofol infusion during painless colonoscopy

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ABSTRACT

Background: Remimazolam tosilate is an ultra-short-acting sedative drug with the advantages of rapid onset and recovery, mild respiratory, and circulatory inhibition. This study primarily investigated the effect of remimazolam on incidence of intraoperative hypotension compared to the widely used propofol in patients undergoing outpatient painless colonoscopy.

Methodology: This was a double-blinded, randomized, controlled trial. We randomly divided the eligible patients with outpatient appointment for painless colonoscopy in our hospital into the remimazolam group and the propofol group. The modified observer's assessment of alert/sedative was used to evaluate the depth of the patient's sedation. The Narcotrend score was monitored throughout the whole process. In the propofol group, propofol 0.5-1.5 mg/kg was infused intravenously as a loading dose, followed by 3-5 mg/kg/h to maintain a satisfied sedation depth during operation. While, with regarding to the patients in remimazolam group, remimazolam 0.05-0.15 mg/kg was induced intravenously as a loading dose, and continuously pumped at a rate of 0.3-0.5 mg/kg/h. SPSS 23.0 software was used to analyze the data.

Results: From December 2020 to March 2021, we enrolled 116 eligible patients. The incidence of hypotension during sedation (13.8%) in the remimazolam group was significantly lower than that in propofol (37.9%), and the success rate of remimazolam (98.3%) was slightly lower than propofol (100.0%), but the awakening time was significantly shorter ($P < 0.001$); The incidence of respiratory inhibition, nausea, vomiting and other adverse events during colonoscopy, remimazolam was significantly lower than that of propofol ($P < 0.05$).

Conclusion: Remimazolam tosilate still has higher circulatory stability than propofol in painless colonoscopy under continuous administration with a loading dose.

Trial registration: The trial was registered at the Chinese Clinical Trial Registry (ChiCTR2000040557), data of registration: December 2020.

Abbreviations: BMI- Body Mass Index; MOAA/S- Modified Observer's Assessment of Alert Scale; MAP- Mean Arterial Pressure; Rem- Remimazolam; Pro- Propofol

Key words: Remimazolam tosilate; Propofol; Painless Colonoscopy; Hypotension

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1. INTRODUCTION

According to data from GLOBOCAN 2018, colorectal cancer is the third most deadly and fourth most commonly diagnosed cancer around the world.[1] By 2030, the worldwide incidence of colorectal cancer is expected to elevate by 60%, and more than 1.1 million of people will die from colorectal cancer.[2] The accurate diagnosis of early-stage of colorectal cancer or precancerous disease is critical to reduce the colorectal cancer related mortality, and gastrointestinal endoscopy remains currently the gold standard for the diagnosis of diseases of digestive tract.[3]

Considering the discomfort from endoscopy, more and more patients select the painless method under certain sedation depth, which also facilitate the operation of the surgeon. Propofol, midazolam or etomidate combined with opioids are mainly used for painless colonoscopy, and the combination of propofol and sufentanil is now the most widely used.[4-6] Although propofol has a rapid onset of sedative effect, it can produce obvious respiratory and circulatory inhibition.[7] The new drug remimazolam tosilate is an ultrashort-acting benzodiazepine, and meanwhile has slight impact on patient's circulation and respiration.[8,9] Therefore, remimazolam may be currently an optimal medicine in patients with painless colonoscopy. According to most of previous studies, remimazolam and propofol were administered intermittently to maintain a sedative depth during the whole endoscopy.[8-10] In this study, we adopted an anesthesia scheme of initial bolus dose to quickly reach a sufficient blood concentration, and then followed by a continuously intraoperative administration.

The primary outcome of this study was to investigate the effect of remimazolam versus propofol on hemodynamics in the process of painless colonoscopy. We therefore tested the primary hypothesis that a continuous administration of remimazolam with an initial bolus dose could significantly reduce the incidence of hypotension in patients undergoing outpatient colonoscopy, compared to propofol. Besides, we also secondarily observed the incidence of hypotension requiring to be managed, heart rate (HR), mean arterial blood pressure (MAP) at the critical time points, the latent period, awakening period, the duration of outpatient discharge and the incidence of other complications such as respiratory depression, dizziness, nausea, vomiting, injection pain, postoperative agitation before hospital discharge.

2. METHODOLOGY

2.1. Study design

This was a single-center, randomized and double-blind trial. This study was approved by the ethics committee of the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi City, Hubei province, China (2020-007-01). We selected the adult patients (aged 18-65 y and ASA grading I-II) who were scheduled to undergo outpatient painless colonoscopy in our center from December 2020 to March 2021. We conducted the trial according to the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. All patients participating in the trial signed the informed consent form.

2.2. Patients' eligibility

Inclusion criteria were patients undergoing painless colonoscopy, ages 18-65 y, ASA PS I-II. Exclusion criteria included the patient refusal to participate in the study; a history of brain surgery; diabetic patients whose fasting blood glucose was 11.1 mmol/l or higher preoperatively; a history of myocardial infarction and unstable angina pectoris within 6 months; bradycardia (heart rate ≤ 50 beats/min), malignant arrhythmia or third degree atrioventricular block (excluding patients using pacemakers) within 6 weeks; the patient with systolic blood pressure ≤ 90 mmHg within 6 weeks; a history of mental disease (such as schizophrenia, depression, epilepsy etc.) or cognitive dysfunction; a history of abuse of psychotropic substances and/or narcotic drugs; abnormal coagulation function (PT or PT-INR > 1.5 times of the normal upper limit, APTT > 1.5 times of the normal upper limit), bleeding tendency (such as active peptic ulcer) or being treated with thrombolysis or anticoagulation; abnormal liver function (ALT and / or AST > 1.5 times of the normal upper limit); abnormal renal function (serum creatinine and / or urea nitrogen

(BUN) > 1.5 times the normal upper limit and/or dialysis); a history of allergy to the tested drugs or one of ingredients of them; pregnant or breast-feeding ladies; and the patient enrolled by other clinical trials within 3 months.

2.3. Randomization and masking

After obtaining informed consent, all eligible patients were randomly allocated into the remimazolam group and propofol group in a ratio of 1:1 by a computer-generated coding system. The codes of patients were placed in the sequentially numbered opaque envelopes. Envelopes were opened shortly before surgery. An anesthesiologist, who did not participate in the study, formulated the drugs. The concentration of propofol was 10 mg/ml, and remimazolam 1 mg/ml. The syringe was wrapped in a black paper with an accurate scale, and the extension tube was also blackened with a black pen to avoid unblinding due to the drug color. The enrolled patients, anesthesiologists, outcome assessors and surgeons were not aware of the treatment assignment.

2.4. Procedures

After endoscopy room admission, the patients were routinely monitored for electrocardiogram (ECG), blood pressure (BP) and pulse blood oxygen saturation (SpO2). Meanwhile, we assessed the sedation depth by the Narcotrend score.[11] and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score,[10] during the whole procedure (Supplementary Table 1). A peripheral venous access was established. All patients received oxygen for 2 L/min by a nasal catheter. In the propofol group, sufentanil 0.1 μg/kg (gyzz h20054171, specification; 1 ml, 50 μg; Yichang Humanwell Pharmaceutical Co., Ltd.) and propofol 0.5-1.5 mg/kg (H20040079; 20 ml, 200 mg; Sichuan Guorui Pharmaceutical Co., Ltd.) were slowly injected intravenously as a bolus dose, followed by propofol 3-5 mg/kg/h to maintain a certain sedation depth during operation. The remimazolam group was induced by bolus intravenous injection of sufentanil 0.1 μg/kg and remimazolam 0.05-0.15 mg/kg (H20190034; 36 mg; Hengrui Pharmaceutical Co., Ltd.), and maintained the same sedation depth as propofol by intravenous pump at a speed of 0.3-0.5 mg/kg/h. We halted the administration of all anesthetics at 10 min before the end of the operations. If the sedation depth of patients during the anesthesia process could not meet the requirements of the operation, propofol 20 mg or remimazolam 2 mg boluses would be added (if more than 5 times were added within 15 min, it would be recorded as sedation failure, and etomidate would be used to remedy sedation). The depth of sedation was MOAA/S ≤ 2 at the time of lens entry and MOAA/S ≤ 3 during the examination. Stable respiration and circulation were maintained during the procedure. If hypotension or bradycardia occurred, ephedrine 10 mg or atropine 0.25-0.5 mg IV were injected. In case of respiratory depression, 100% oxygen by mask was administered with hand control or mechanical ventilation. After the examination, all patients were sent to the observation room for further monitoring, and they were discharged home when Chung's Departure Score exceeded 9 points.[12]

2.5. Outcomes

Primary outcome: the incidence of hypotension during the colonoscopy procedure.

Secondary outcomes: 1) hypotension requiring to be managed; 2) the heart rate (HR), mean arterial blood pressure (MAP), and SpO_2 recorded at the following time points: endoscopy room admission (T0), anesthesia induction completion (T1), endoscopy into the anus (T2), enteroscopy to ileocecal part (T3), at the end of surgery (T4), 5 min after surgery (T5); 3) the latent period, the awakening period, the duration of outpatient discharge; 4) and the incidence of adverse events such as respiratory depression, dizziness, nausea, vomiting, injection pain, postoperative agitation before leaving the hospital. A single investigator blinded to the group allocation recorded all measurements.

2.6. Evaluation criteria

(1) Hypotension: systolic pressure < 90 mmHg or systolic blood pressure < 20% of the baseline value during the period from the initiation of drug administration to the complete recovery after drug withdrawal.
(2) Bradycardia: HR < 50 beats/min; (3) Respiratory depression: respiratory frequency < 8 breaths/min or SpO_2 < 90%; (4) Latent period: the duration from the start of drug administration to the first MOAA/S ≤ 2; (5) Awakening period: the duration from the suspension of drug infusion to the first MOAA/S = 5; (6) The duration of outpatient discharge: the duration from full awaking to Chung's ≥ 9 points; (7) Sedative efficacy, e.g., successful completion of colonoscopy, MOAA/S ≤ 3 points during colonoscopy, and no use of any other sedatives.

2.7. Statistical analysis

PASS 15.0 software (NCSS, Kaysville, UT) was used to estimate the sample size. According to the previous studies, the incidence of remimazolam related hypotension in painless gastrointestinal endoscopic sedation anesthesia was 13.03%, while the incidence of propofol related hypotension was 42.86% under intermittent drug administration or boluses.[15] In this tudy, $\alpha = 0.05$, $\beta = 0.9$, considering a 20% loss of follow-up, the final sample size of each group was 56 cases. SPSS 23.0 statistical software (IBM Co., Armonk, NY, USA) was used for statistical analyses. 23.0 statistical software

(IBM Co., Armonk, NY, USA) was used for statistical analyses. The continuous data in line with the normal distribution are shown by the mean ± standard deviation (SD), and the inter-group comparison was performed by independent sample t test, and the repeated measurement data at different time points was analyzed by repeated measurement variance analysis. The data with abnormal distribution are represented by median and interquartile range (IQR), and compared using the Mann–Whitney U test. The categorical data are represented by a percentage (%), and their comparisons between two groups are determined by the Chi-square test, Fisher's exact test or Wilcoxon rank-sum test. Kaplan–Meier analyses are used for time-to-event outcomes.
$P < 0.05$ is considered statistically significant.

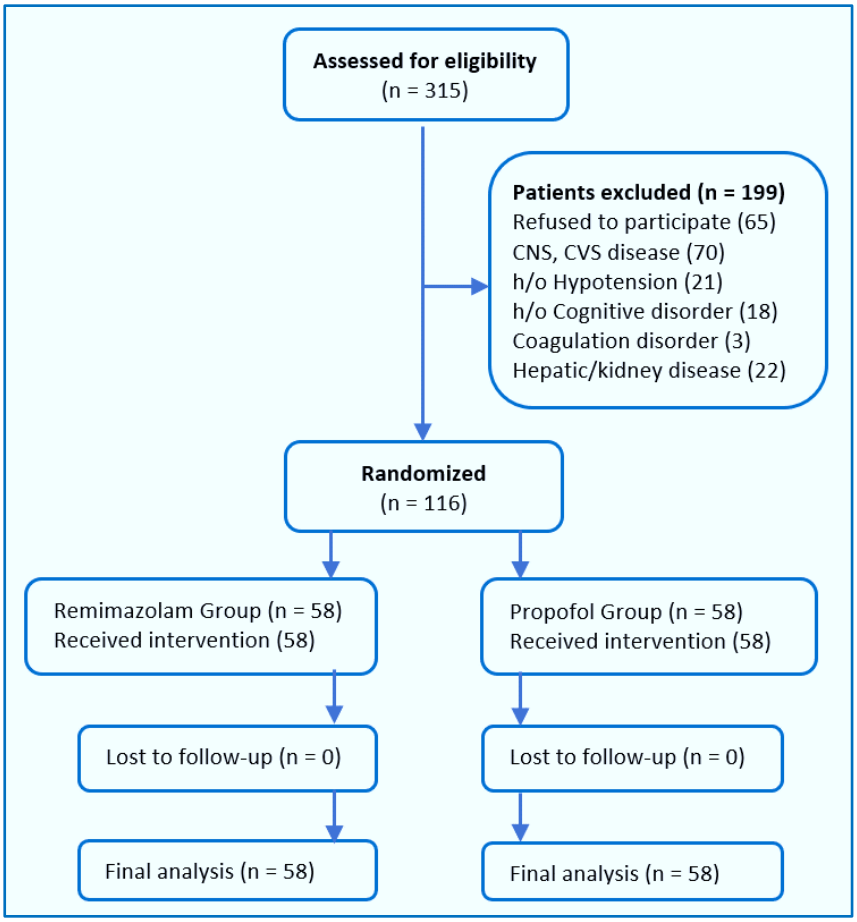

Figure 1: Study flow chart

3. RESULTS

A total of 116 patients were enrolled after screening 315 patients who were expected to have outpatient colonoscopy under sedation from December 2020 to March 2021. Out of 116 participants, 58 patients were randomly allocated into remimazolam group, and 58 into propofol group (Figure 1).

The baseline characteristics between the two groups were well balanced for the age, gender, height, BMI, ASA score, and other demographics (Table 1).

The primary outcome

Eight patients (13.8%) in the remimazolam group and 22 (37.9%) in the propofol group developed hypotension during colonoscopy, and the incidence of hypotension in the remimazolam group was significantly lower than that in the propofol group ($P < 0.001$(Table 2).

Table 1: Comparison of baseline data between the two groups (n = 58)

Parameter	Remimazolam	Propofol	t/χ^2	*p*
ASA I/II (n)	32/26	37/21	2.962	0.085
Gender (male/female) (n)	35/23	31/27	1.793	0.181
Height (cm)	162.83 ± 7.733	160.26 ± 8.271	1.728	0.087
Weight (kg)	61.12 ± 9.795	62.81 ± 8.338	-1.000	0.319
BMI (kg/m^2)	23.18 ± 4.212	24.71 ± 4.521	-1.888	0.062
Age (y)	48.64 ± 8.983	47.19 ± 11.917	0.739	0.461
Operation duration (min)	20.05 ± 5.309	19.84 ± 5.486	0.206	0.837
Infusion volume (ml)	166.42 ± 40.068	164.71 ± 45.535	0.206	0.837

Data presented as numbers or mean ± SD

Table 2: Comparison of the primary and secondary outcomes between the two groups (n = 58)

Items	Remimazolam	Propofol	t/χ2	P
Primary outcome				
Hypotension	8 (13.8%)	22 (37.9%)	30.255	0.000
Secondary outcomes				
Hypotension needs treatment	3 (5.2)	11 (19.0)	20.893	0.000
Latent time（s）	138.95 ± 37.961	95.69 ± 44.666	5.592	0.000
Awakening period（min）	6.91 ± 2.558	8.41 ± 2.878	-2.955	0.004
The duration of outpatient discharge (min)	9.38 ± 3.283	13.74 ± 3.552	-6.826	0.000
• The incidence of respiratory depression	1 (1.7)	15 (25.9)	57.795	0.000
• Nausea	7 (12.1)	13 (22.4)	8.576	0.003
• Vomiting	2 (3.4)	1 (1.7)	1.360	0.243
• Dizziness	13 (22.4)	21 (36.2)	9.727	0.002
• The injection pain	2 (3.4)	25 (43.1)	83.749	0.000
• Bradycardia	1 (1.7)	6 (10.3)	15.434	0.000

Data presented as mean ± SD or n (%)

Table 3: Comparison of HR, MAP and SpO_2 at each time point (n = 58, mean ± SD)

Items	Group	T0	T1	T2	T3	T4	T5
		79.1 ± 12.8	77.3 ± 13.3*	73.1 ± 14.9*	72.7 ± 14.7*	72.9 ± 12.8*	75.7 ± 12.1
HR	Pro	76.1 ± 11.3	70.1 ± 10.0	65.5 ± 10.8	66.9 ± 11.2	66.9 ± 11.2	68.9 ± 11.5
	F_g = 8.90, P_g = 0.003 $F_{t\times g}$ = 2.868, $P_{t\times g}$ = 0.032 F_t = 41.582, P_t = 0.000						
	Rem	84.5 ± 10.5	81.3 ± 9.7*	76.8 ± 10.5*	77.8 ± 10.8	78.6 ± 10.4	82.1 ± 8.9
MAP	Pro	88.3 ± 11.4	65.0 ± 11.4	68.3 ± 11.8	74.3 ± 8.2	74.3 ± 8.2	85.3 ± 8.9
	F_g = 4.017, P_g = 0.047; $F_{t\times g}$ = 59.730, $P_{t\times g}$ = 0.000 ; F_t = 122.81, P_t = 0.000						
	Rem	99.8 ± 0.7	99.7 ± 0.9*	99.6 ± 1.2*	99.8 ± 1.3*	99.9 ± 0.5*	99.9 ± 0.7
SpO_2	Pro	99.7 ± 0.9	94.0 ± 8.5	98.0 ± 4.9	98.8 ± 3.2	99.6 ± 1.0	99.9 ± 0.5
	F_g = 37.972, P_g = 0.000 ; $F_{t\times g}$ = 16.173, $P_{t\times g}$ = 0.000 ; F_t = 17.124, P_t = 0.000						

*Notes: *P means at the same time point, compared with propofol group, P < 0.05.Fg ,Pg means comparison between groups, Ft×g,Pt×g means interaction effect between time and groups, Ft, Pt means comparison of the different time points.*

The secondary outcomes

The incidence of patients with remimazolam group who required treatment for hypotension (5.2%) was significantly lower than that in the propofol group (19.0%) (P < 0.001) (Table 2).

The latent time of remimazolam (138.95 ± 37.96S) was strikingly longer than that of propofol group (95.69 ± 44.67S) (P < 0.001), but the awakening period and the duration of outpatient discharge were significantly shorter than that of propofol group (P = 0.004 and P < 0.001) (Table2).

After the completion of anesthesia induction, HR, MAP and SpO_2 of the two groups experienced a trend of decline first and then increasing gradually, and their lower values were mainly found at T_1, T_2 time points.

Compared with propofol, the changes of HR, MAP and SpO_2 in remimazolam group were relatively small, and the difference was statistically significant. ($P_{intergroup}$ = 0.044, $P_{intergroup}$ = 0.045, $P_{intergroup}$ = 0.000, and there is an interaction between time and grouping ($P_{time\times intergroup}$ > 0.05) (Table 3).

Under the premise of no statistical differences in the depth of anesthesia, after completion of induction, MOAA/S scores of the two groups first declined and then gradually increased, and the lowest value mainly was found at T2, T3. Compared with propofol group, the MOAA/S scores T4 and T5 in the remimazolam group were significantly higher, and the difference was statistically significant (P < 0.05) (Supplementary Table 1 and 2).

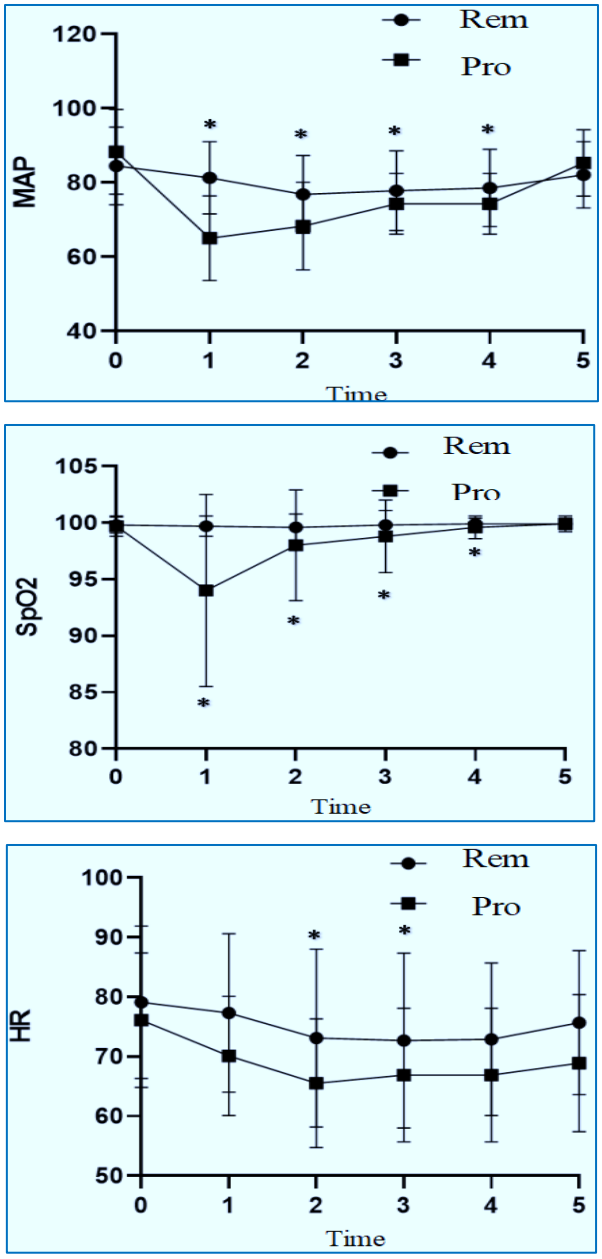

Figure 2: Comparison of MAP, SpO_2 and HR

(Notes: *P means at the same time point, compared with propofol group, P < 0.05)

There was no statistical difference in incidence of other complications (P < 0.05) except for vomiting (P > 0.05) between the two groups (Table 2).

4. DISCUSSION

The results of our study show that the incidence of hypotension in the remimazolam group was significantly lower than that in the propofol group during colonoscopy under the similar depth of sedation between the two

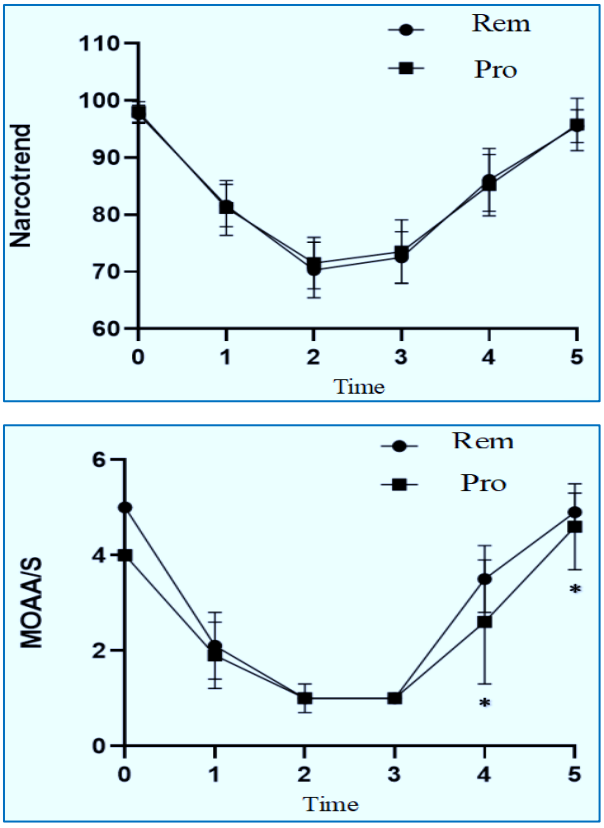

Figure 3: Comparison of MOAA/S, Narcotrend

groups. Compared to propofol, awakening period and the duration of outpatient discharge were both significantly shorter in patients receiving remimazolam. Besides, we observed the values of MAP, HR and SpO_2 at six critical time points of colonoscopy procedures, and found that the changes of HR, MAP and SpO_2 in remimazolam group were considerably mild. Meanwhile, the incidence of complications such as respiratory depression, dizziness, nausea, injection pain and awareness during the sedation process were also significantly lower in remimazolam than propofol group separately.

Remimazolam may be an optimal substitute for propofol. Propofol, as the preferred drug for gastrointestinal endoscopy has the satisfactory sedation effect, but its side effects are obvious, including pain on injection, and dose-dependent circulation and respiratory inhibition.[13-16] The combination of propofol and ketamine or opioids can significantly reduce the dose of propofol, thus producing less incidence of adverse circulatory and respiratory events.[17,18] Therefore, propofol has great shortcomings in the patients with cardiopulmonary insufficiency. Remimazolam, as an analog of midazolam, is a water-soluble sedative, and has the pharmacological features of rapid onset and elimination because it can rapidly be hydrolyzed to inactivate metabolites by non-specific tissue esterase.[19]

Table 1 (Sup): Comparison of sedation success rate (n = 58)

Parameters	Remimazolam	Propofol	χ2	P
Sedation successful	57 (98.3)	58 (100)	4.	0.
MOAA/S≤3 points during colonoscopy	57 (98.3)	58 (100)	4.	0.
Successful completion of the colonoscopy	58 (100)	58 (100)		
Sedation without remedy	58 (100)	58 (100)		

Table 2 (Sup): Comparison of MOAA/S、Narcotrend score at each time point (n = 58, mean ± SD)

Items	Group	T0	T1	T2	T3	T4	T5
MOAA/S score	Rem	5.0 ± 0.0	2.1 ± 0.7	1.0 ± 0.3	1.0 ± 0.0	3.5 ± 0.7*	4.9 ± 0.4*
	Pro	4.9 ± 0.1	1.9 ± 0.7	1.0 ± 0.0	1.0 ± 0.1	2.6 ± 1.3	4.6 ± 0.9
		Fg = 23.003, Pg = 0.000 ; Ft×g = 11.210, Pt×g = 0.000 ; Ft = 1112.95, Pt = 0.000					
Narcotrend score	Rem	97.6 ± 1.6	81.6 ± 3.7	70.3 ± 4.9	72.5 ± 4.5	86.1 ± 5.5	95.5 ± 2.9
	Pro	98.0 ± 1.8	81.2 ± 4.8	71.5 ± 4.5	73.5 ± 5.6	85.2 ± 5.4	95.8 ± 4.6
		Fg = 0.310, Pg = 0.579 ; Ft×g = 1.016, Pt×g = 0.396 ; Ft = 836.345, Pt = 0.000					

A study observed twenty healthy male volunteers (ages 20-38 y, weight 64-99 kg) receiving remimazolam as continuous intravenous infusion of 5 mg/min for 5 min, 3 mg/min for the next 15 min, and 1 mg/min for further 15 min, and concluded that remimazolam showed a high clearance (1.15 ± 0.12 L/min), a small steady-state volume of distribution, 35.4 ± 4.2 L, and a short terminal half-life, 70 ± 10 min.[20]

Meanwhile, MAP reduced by 24 ± 6%, HR elevated by 28 ± 15%, and spontaneous breathing was maintained throughout the whole procedure.[21] Some clinical studies proved that patients with remimazolam showed more stable hemodynamic effects; however, remimazolam slightly affected patients' respiration under the routine clinical sedative dose during their surgical procedures.[20-23]

This study provided more reliable evidence for the use of remimazolam as the best option for patients receiving outpatient painless endoscopy. In previous studies, the initial dose at induction and a single-dose later on, were mostly used to maintain the sedation depth of MOAA/S ≤ 3 points at implantation of endoscopy, and MOAA/S ≤ 4 points at the whole procedure.[23,24] In this study, we took an anesthesia scheme with an initial dose and then continuous intraoperative infusion to reach the sedation depth of MOAA/S ≤ 2 points at implantation of endoscopy, and MOAA/S≤ 3 points during the whole colonoscopy. In the pre-experimental stage, we found that at MOAA/S > 3, a higher proportion of patients were stimulated by pain and woke up, which made endoscopy difficult or even impossible. Therefore, we moderately deepened the depth of sedation, which may theoretically increase the incidence the respiratory and circulatory inhibition. However, our results suggested that the blood concentration was more stable and there was no circulatory fluctuation. The circulation fluctuation was small through continuous administration of remimazolam with a loading dose, and maintenance of a satisfied sedation depth. The results of our study might provide important evidence on doses of remimazolam and sedation depth in colonoscopy. Secondly, we monitored the Narcotrend score throughout the whole process. It is more convincing to evaluate the latent time, awakening period and the duration of outpatient discharge under the premise that there is no difference in the depth of anesthesia between the two groups.

5. LIMITATIONS

The study had several limitations. Firstly, we enrolled the patient aged 18-65 years, and could not assess the safety and validity of remimazolam in the elderly (> 65 y) and children (< 18 y). Secondly, we did not acquire the data on safety and validity of the patients after outpatient discharge; as long-term outcomes may be different. Thirdly, we obtained the depth of sedation by the subjective method, which might produce measurement bias, and thereby interfere the accuracy of results. Fourthly, the data of this trial was generated from a single center. An RCT with multiple centers and large sample size may be required to further testify these results.

6. CONCLUSION

In summary, compared to propofol, remimazolam could offer more stable hemodynamics in adult patients undergoing painless colonoscopy at the same depth of sedation. Despite the continuous pump infusion,

remimazolam tosilate still has higher circulatory stability than propofol in painless colonoscopy. Besides, remimazolam might significantly decrease the incidence of adverse effects such as respiratory depression, nausea, and arrhythmia. Therefore, we conclude that remimazolam is an effective and safe agent in patients undergoing outpatient colonoscopy.

7. Data availability

All data generated or analyzed during this study are included in this published article.

8. Funding

This work was funded by the Clinical Research Special Foundation of Hubei Chen Xiaoping Science and Technology Development Foundation (Number: cxpJJH12000005-07-20).

9. Ethical approval / consent to participate

All the experiments in this study were conducted in accordance to relevant guidelines and regulations. This study was approved by the ethics committee of the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi City, Hubei province, China (2020-007-01). All patients participating in the trial signed the informed consent form.

10. Competing interest

All authors declare no conflict of interests.

11. Acknowledgments

This work was supported by the Clinical Research Special Foundation of Hubei Chen Xiaoping Science and Technology Development Foundation (Number: cxpJJH12000005-07-20).

12. Supplementary materials

Supplementary Table 1 was the comparison of sedation success rate; Supplemenatry Table 2 was the comparison of MOAA/S、Narcotrend score at each time.

13. Authors' contributions

XZ, SL: Literature search; Analyzed the data; drafted the manuscript.

YZ, GY and NY: Literature review; Offered critical analysis of the manuscript.

HW: Oversaw this project and revised the manuscript.

All authors have read and approved the final manuscript.

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