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Effects of Remimazolam Dose and Bolus Injection Rate on Hiccups During Painless Colonoscopy: A Double-Blind Randomized Clinical Trial

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Background: Remimazolam is increasingly used for procedural sedation because of its rapid onset, rapid recovery and favourable haemodynamic profile. However, hiccups remain a clinically relevant adverse event that may interfere with endoscopic manipulation. The independent and combined effects of remimazolam dose and injection rate on hiccup occurrence have not been well characterized.

Methods: In this prospective, randomized, double-blind, 2×2 factorial trial, adult patients undergoing painless colonoscopy were randomized to receive remimazolam at 0.3 or 0.4 mg kg^{-1}, administered over 10s or 20s. The primary endpoint was hiccup incidence. Secondary endpoints included body movement, supplemental bolus requirements, time to loss of eyelash reflex, recovery time, haemodynamic changes, Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores and postoperative Numeric Rating Scale (NRS) scores. Multivariable logistic regression evaluated the independent effects of dose and injection rate on hiccup incidence and tested for interaction.

Results: Both the higher remimazolam dose (0.4 mg kg^{-1}) and the slower bolus injection rate (20s) were independently associated with a lower incidence of hiccups. After adjustment for age, sex, body mass index, smoking status, hypertension and diabetes, the 0.4 mg kg^{-1} regimen showed lower odds of hiccups than the 0.3 mg kg^{-1} regimen, and 20s administration showed lower odds than 10s. No significant dose × rate interaction was detected. The higher-dose regimen was additionally associated with fewer body movements and supplemental boluses, without increased haemodynamic compromise.

Conclusion: Both a higher remimazolam dose and a slower bolus injection rate were independently associated with a lower incidence of hiccups during painless colonoscopy. Remimazolam 0.4 mg kg^{-1} administered over 20s may offer the most favourable balance between hiccup prevention, procedural conditions and haemodynamic stability.

Keywords: remimazolam, hiccups, colonoscopy, injection rate, factorial trial

Introduction

Painless colonoscopy is widely used to improve patient comfort, procedural tolerance and endoscopist working conditions. The choice of sedative regimen therefore requires a careful balance between sedation quality, recovery profile and cardiopulmonary safety.[1–3] Remimazolam, an ultra-short-acting intravenous benzodiazepine, has attracted increasing attention in procedural sedation because of its rapid onset, fast recovery, and relatively stable haemodynamic and respiratory profile compared with conventional agents.[4–8]

Despite these advantages, remimazolam-associated hiccups have emerged as a clinically relevant adverse event. Hiccups may interrupt endoscopic manipulation, compromise procedural smoothness and reduce operating conditions for the endoscopist.[9–11] Pathophysiologically, hiccups are generally considered a myoclonic-like phenomenon mediated by a brainstem reflex arc involving afferent, central and efferent neural pathways, and may be modulated by GABAergic and serotonergic mechanisms.[9,12–14] Recent case reports and reviews have suggested that remimazolam may precipitate hiccups or other paradoxical neurobehavioural responses in susceptible individuals.[10,11,15]

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Dose selection is known to influence both sedation adequacy and adverse-event profiles,[16–19] while pharmacokinetic and pharmacodynamic studies suggest that bolus administration rate may shape early peak drug exposure and effect-site concentration dynamics.[8,20–22] However, the independent and combined effects of remimazolam dose and injection duration on hiccups during painless colonoscopy remain unclear. We therefore conducted a prospective, randomized, double-blind, 2×2 factorial trial to evaluate whether remimazolam dose (0.3 versus 0.4 mg kg^{-1}) and bolus injection duration (10 versus 20s) independently or jointly affect the incidence of hiccups during painless colonoscopy.

Methods

Study Design and Participants

We conducted a prospective, randomized, double-blind, controlled 2×2 factorial trial between April and December 2025. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Clinical Medical Research Ethics Committee of Chengdu Integrated TCM & Western Medicine Hospital (Approval No. 2025-KT-002) and registered with the Chinese Clinical Trial Registry (ChiCTR2500099326). Written informed consent was obtained from all participants before enrolment. Eligible participants were adults aged 18–65 years with American Society of Anesthesiologists (ASA) physical status I–III who were scheduled to undergo elective colonoscopy (ie. colonoscopy under sedation, including both diagnostic and therapeutic procedures) with an anticipated duration of 30 min or less. Exclusion criteria were known hypersensitivity to study medications, chronic use of psychotropic drugs for psychiatric disorders, anticipated difficult airway, recent infection, major surgery or trauma within 1 month, ASA physical status IV or V, hepatic dysfunction, and any condition judged by the investigators to make trial participation unsuitable.

Randomization and Blinding

Participants were randomly assigned in a 1:1:1:1 ratio to one of four treatment groups according to remimazolam dose and bolus injection duration: 0.3 mg kg^{-1} over 10s (Group A1), 0.3 mg kg^{-1} over 20s (Group A2), 0.4 mg kg^{-1} over 10s (Group B1), or 0.4 mg kg^{-1} over 20s (Group B2). The randomization sequence was generated by an independent statistician using computer-generated block randomization. Allocation was concealed using sequentially numbered, opaque, sealed envelopes. An independent unblinded anaesthesia nurse opened the envelope after baseline assessment, prepared the study drug in a separate room, and delivered the assigned bolus over the allocated 10-s or 20-s interval. Remimazolam was diluted with normal saline to a total volume of 20 mL to ensure identical syringe appearance across groups. Participants, endoscopists, outcome assessors and the clinical staff responsible for intraoperative monitoring and data collection remained blinded to treatment allocation.

Clinical Protocol

All procedures were conducted according to standardized departmental anaesthesia protocols. Patients received intravenous Ringer's acetate for baseline hydration and routine preoxygenation via nasal cannula at 2 L min^{-1} in the preparation area. Standard monitoring included a 5-lead electrocardiogram, heart rate (HR), peripheral oxygen saturation (SpO2) and respiratory rate. After preoxygenation, patients received a single intravenous induction bolus of remimazolam (25 mg per vial; Jiangsu Hengrui Medicine Co., Ltd.) at the allocated dose and injection duration. If additional sedation was required during the procedure, supplemental remimazolam boluses of 2.5 mg were administered.

Outcomes

The primary endpoint was the incidence of hiccups during the procedure. Hiccups were defined as involuntary, audible, spasmodic contractions of the diaphragm occurring after the start of remimazolam injection and before the end of the procedure. Each discrete episode was identified by the attending anaesthesiologist based on direct visual and auditory observation. A hiccup episode was defined as one or more consecutive hiccup contractions separated from any subsequent episode by a hiccup-free interval of at least 30s. The total duration of each episode was recorded in seconds from the first contraction to the last. Secondary endpoints included the frequency of supplemental bolus administration,

frequency of body movement, time to loss of eyelash reflex, recovery time, haemodynamic changes (HR, systolic blood pressure and diastolic blood pressure), MOAA/S scores and postoperative NRS scores. Hiccup duration was analysed only among participants who experienced hiccups.

Sample Size Calculation

Sample size estimation was based on pilot data showing that the incidence of hiccups was 31–52% in patients receiving remimazolam 0.3 mg kg^{-1} and <5% in those receiving 0.4 mg kg^{-1}. With a two-sided type I error rate of 0.05 and 80% power, the minimum required sample size was calculated to be 36 participants per group. Assuming a 20% dropout rate, the target enrolment was increased to 43 participants per group. The trial was primarily powered for between-group differences in hiccup incidence, while analyses of interaction and secondary endpoints were considered exploratory.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0. Continuous variables were reported as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were reported as counts and percentages. Baseline characteristics were summarized descriptively. The primary analysis followed the prespecified factorial design and focused on the main effects of remimazolam dose and injection duration, as well as their interaction, on hiccup incidence. An unconditional binary logistic regression model was used to evaluate these associations while adjusting for potential confounders, including age, sex, body mass index, smoking status, hypertension and diabetes. Because a baseline age imbalance was observed between pooled dose groups, age was retained as a covariate in the multivariable model. Secondary outcomes were considered supportive and exploratory. No formal adjustment for multiplicity was applied to secondary or subgroup comparisons, which should therefore be interpreted cautiously. Because some secondary endpoints were non-normally distributed, non-parametric methods were used without covariate adjustment. A two-sided P value < 0.05 was considered statistically significant.

Results

Patient Enrollment

A total of 172 patients scheduled for painless colonoscopy were screened for eligibility. Two declined participation, leaving 170 patients for randomization. These patients were assigned to Group A1 (n = 43), Group A2 (n = 43), Group B1 (n = 42) and Group B2 (n = 42). After randomization, 7 patients were excluded for the following reasons: suspension of the procedure because of an unanticipated difficult airway (n = 1), procedure duration >30 min (n = 2), pre-induction blood pressure >180/110 mmHg (n = 1), poor bowel preparation leading to suspension of the procedure (n = 2), and arrhythmia before induction (n = 1). Ultimately, 163 patients received their allocated intervention and were included in the final analysis: 40 in Group A1, 41 in Group A2, 41 in Group B1 and 41 in Group B2 (Figure 1).

Baseline Characteristics

For baseline description, subgroups A1 and A2 were pooled as Group A, and subgroups B1 and B2 were pooled as Group B according to remimazolam dose. Baseline characteristics were broadly similar across the pooled groups with respect to body mass index, sex distribution, smoking history, hypertension, diabetes and pre-induction haemodynamic variables. Participants in Group A were, on average, older than those in Group B; age was therefore included as a covariate in the multivariable analysis of the primary outcome (Table 1).

Primary Outcome

Group-level and exploratory subgroup results are presented in Tables 2–6, respectively. In the prespecified factorial analysis, both remimazolam dose and injection duration were independently associated with hiccup incidence, whereas no significant dose-by-rate interaction was detected. Specifically, compared with 0.3 mg kg−1, the 0.4 mg kg−1 regimen was associated with lower odds of hiccups (odds ratio [OR] = 0.376, 95% confidence interval [CI] 0.177–0.800). Similarly, administration over 20s was associated with lower odds of hiccups than administration

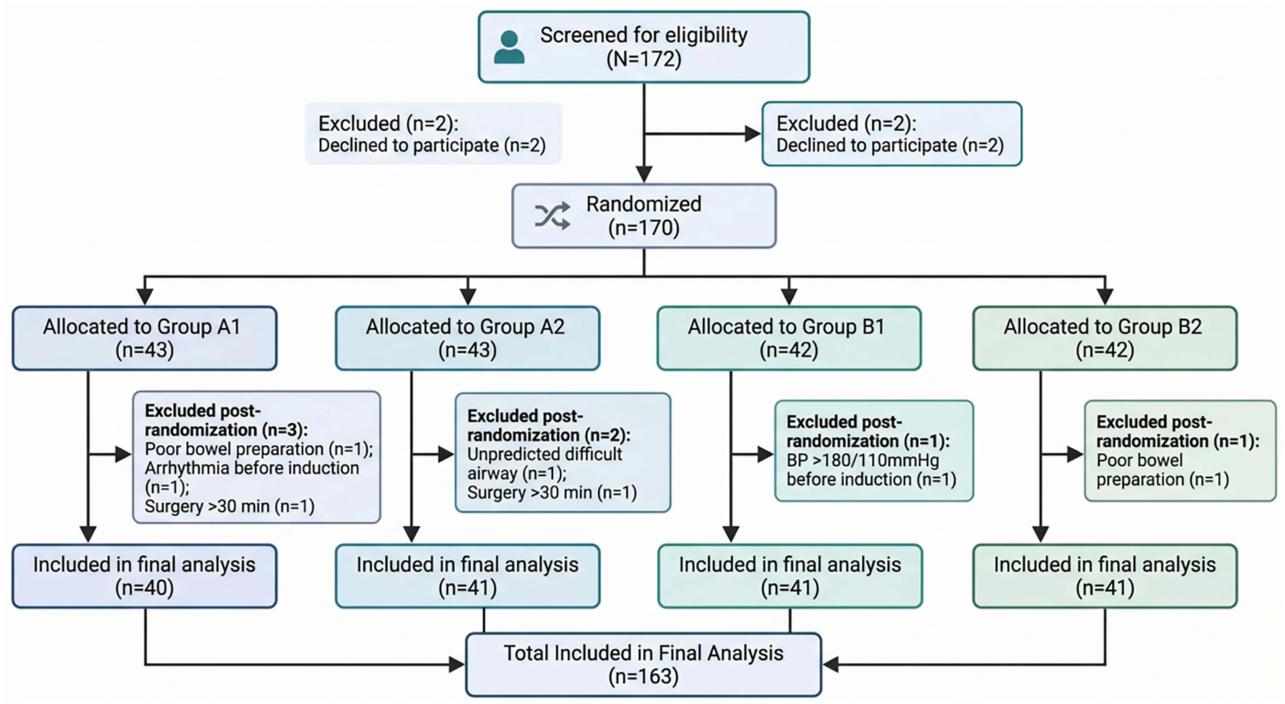

Figure 1 Flowchart of patient recruitment.

over 10s (OR = 0.240, 95% CI 0.114–0.505). To explore potential synergistic or antagonistic effects, an interaction term between remimazolam dose and injection duration was initially included in the model. No statistically significant interaction was observed (P = 0.598), and the final parsimonious model therefore retained the two main effects. These findings indicate that dose and injection duration contributed independently to hiccup risk in this study (Table 7).

Table 1 Comparison of Pre-Induction Baseline Characteristics Between Groups

Variable	Group A (n=81)	Group B (n=82)	t	P
Age (years)	49.4±12.9	44.1±12.9	2.649	0.009
BMI	23.7±2.8	23.5±2.1	0.436	0.664
Sex (Male/Female)	37/44	36/46	0.052	0.820a
Smoking, n (%)	13(16.0)	16(19.5)	0.334	0.563a
Hypertension, n (%)	16(19.8)	17(20.7)	0.024	0.876a
Diabetes, n (%)	6(7.4)	6(7.3)	0.000	0.982a
Pre-induction HR (beats/min)	72.7±10.1	73.4±8.7	0.456	0.649
Pre-induction SBP (mmHg)	125.5±13.8	122.9±11.5	1.268	0.207
Pre-induction DBP (mmHg)	72.3±9.2	73.9±9.8	1.115	0.266

Notes: Data are presented as mean±SD, n, or n (%). [a]Analyzed using the Chi-square test for two independent samples. Age was adjusted for in the multivariable analysis.
Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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Table 2 Comparison of Post-Injection Effects Between Groups

Variable	Group A (n = 81)	Group B (n = 82)	*Z*	*P*
Hiccups, n (%)	34(42.0)	21(25.6)	4.882	0.027a
Hiccup duration (s)	12.5±3.9	15.1±5.9	3.272	0.001b
Number of supplemental boluses (n)	1.0(1.0, 1.0)	1.0(0.0, 1.0)	3.029	0.002
Body movements (n)	1.0(0.0, 1.0)	0.0(0.0, 1.0)	3.368	0.001
NRS score	0.0(0.0, 1.0)	0.0(0.0, 0.0)	2.173	0.030
MOAA/S score	1.0(0.0, 1.0)	0.0(0.0, 1.0)	2.283	0.022
Time to loss of eyelash reflex (s)	15.0(12.0,23.0)	16.0(13.0,20.0)	0.772	0.440
Recovery time (min)	5.0(4.0,8.0)	5.0(4.0,7.0)	0.467	0.641
Colonoscopy duration (min)	20.4±5.4	18.6±4.8	2.141	0.034
Anesthesia time (min)	26.7±6.8	24.6±5.9	2.081	0.039
HR reduction (beats/min)	4.0(2.0,8.0)	3.0(2.0,5.0)	1.644	0.100
SBP reduction (mmHg)	6.0(3.5,13.0)	7.5(4.8,10.0)	0.238	0.812
DBP reduction (mmHg)	5.0(2.0,10.0)	5.0(2.0,6.0)	0.956	0.339

Notes: a, Chi-square test; b, independent-samples *t*-test.

Table 3 Comparison of Post-Injection Effects Between Dose Groups Under the 10-s Injection Rate

Variable	Group A1 (n = 40)	Group B1 (n = 41)	*Z*	*P*
Hiccups, n (%)	23(57.5)	16(39.0)	2.768	0.096a
Hiccup duration (s)	9.2±1.3	9.7±0.8	1.965	0.052b
Number of supplemental boluses (n)	1.0(1.0, 1.8)	1.0(0.0, 1.0)	2.492	0.013
Body movements (n)	1.0(1.0, 1.0)	0.0(0.0, 1.0)	3.277	0.001
NRS score	0.0(0.0, 2.0)	0.0(0.0, 0.0)	2.561	0.010
MOAA/S score	1.0(0.0, 1.0)	0.0(0.0, 1.0)	1.679	0.093
Time to loss of eyelash reflex (s)	23.0(19.0,25.0)	19.0(17.0,20.5)	3.596	<0.001
Recovery time (min)	7.0(5.3,10.0)	6.0(5.0,7.5)	2.243	0.025
HR reduction (beats/min)	5.5(3.0,9.0)	3.0(3.0,3.0)	2.391	0.017
SBP reduction (mmHg)	10.0(5.0,17.8)	8.0(7.0,10.0)	0.859	0.390
DBP reduction (mmHg)	5.5(4.0,10.8)	5.0(4.0,6.5)	1.313	0.189

Notes: a, Chi-square test; b, independent-samples *t*-test. These comparisons are exploratory.

Secondary Outcomes

Secondary analyses provided supportive evidence for the primary findings. The higher-dose regimen was associated with fewer body movements and fewer supplemental boluses, suggesting more complete and stable procedural sedation. Slower injection was associated with a lower overall incidence of hiccups, although among the patients who developed hiccups, episode duration was longer in the 20-s injection groups. Haemodynamic changes were not materially different

Table 4 Comparison of Post-Injection Effects Between Dose Groups Under the 20-s Injection Rate

Variable	Group A2 (n = 41)	Group B2 (n = 41)	*Z*	*P*
Hiccups, n (%)	11(26.8)	5(12.2)	2.795	0.095a
Hiccup duration (s)	15.8±2.6	20.5±3.1	7.490	0.001b
Number of supplemental boluses (n)	1.0(0.0, 1.0)	0.0(0.0, 1.0)	1.762	0.078
Body movements (n)	0.0(0.0, 1.0)	0.0(0.0, 1.0)	1.605	0.108
NRS score	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.329	0.742
MOAA/S score	0.0(0.0, 1.0)	0.0(0.0, 0.0)	1.710	0.087
Time to loss of eyelash reflex (s)	13.0(12.0,14.0)	13.0(12.0,15.5)	1.066	0.287
Recovery time (min)	5.0(4.0,5.0)	5.0(4.0,6.0)	0.711	0.477
HR reduction (beats/min)	3.0(2.0,6.0)	3.0(2.0,5.0)	0.318	0.751
SBP reduction (mmHg)	5.0(3.0,10.0)	6.0(3.0,9.5)	0.065	0.948
DBP reduction (mmHg)	3.0(0.0,6.0)	3.0(−0.5,7.0)	0.456	0.649

Notes: a, Chi-square test; b, independent-samples *t*-test. These comparisons are exploratory.

Table 5 Comparison of Post-Injection Effects Between Injection Rates at the 0.3 mg kg^{-1} Dose

Variable	Group A1 (n = 40)	Group A2 (n = 41)	*Z*	*P*
Hiccups, n (%)	23(57.5)	11(26.8)	7.820	0.005a
Hiccup duration (s)	9.2±1.3	15.8±2.6	14.349	<0.001b
Number of supplemental boluses (n)	1.0(1.0, 1.8)	1.0(0.0, 1.0)	2.456	0.014
Body movements (n)	1.0(1.0, 1.0)	0.0(0.0, 1.0)	3.654	<0.001
NRS score	0.0(0.0, 2.0)	0.0(0.0, 0.0)	3.037	0.002
MOAA/S score	1.0(0.0, 1.0)	0.0(0.0, 1.0)	2.541	0.011
Time to loss of eyelash reflex (s)	23.0(19.0,25.0)	13.0(12.0,14.0)	6.306	<0.001
Recovery time (min)	7.0(5.3,10.0)	5.0(4.0,5.0)	4.406	<0.001
HR reduction (beats/min)	5.5(3.0,9.0)	3.0(2.0,6.0)	1.930	0.054
SBP reduction (mmHg)	10.0(5.0,17.8)	5.0(3.0,10.0)	2.608	0.009
DBP reduction (mmHg)	5.5(4.0,10.8)	3.0(0.0,6.0)	3.085	0.002

Notes: a, Chi-square test; b, independent-samples *t*-test. These comparisons are exploratory.

across regimens, and no clear evidence of increased haemodynamic compromise was observed with the higher dose (Table 2). Detailed comparisons across the four individual treatment groups are shown in Tables 3–6 and should be interpreted as exploratory.

Discussion

In this randomized, double-blind, 2×2 factorial trial, both a higher remimazolam dose (0.4 mg kg^{-1}) and a slower bolus injection rate (20s) were independently associated with a lower incidence of hiccups during painless colonoscopy. The

Table 6 Comparison of Post-Injection Effects Between Injection Rates at the 0.4 mg kg^{-1} Dose

Variable	Group B1 (n = 41)	Group B2 (n = 41)	*Z*	*P*
Hiccups, n (%)	16(39.0)	5(12.2)	7.746	0.005a
Hiccup duration (s)	9.7±0.8	20.5±3.1	21.909	<0.001b
Number of supplemental boluses (n)	1.0(0.0, 1.0)	0.0(0.0, 1.0)	1.487	0.137
Body movements (n)	0.0(0.0, 1.0)	0.0(0.0, 1.0)	1.582	0.114
NRS score	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.889	0.374
MOAA/S score	0.0(0.0, 1.0)	0.0(0.0, 0.0)	2.569	0.010
Time to loss of eyelash reflex (s)	19.0(17.0,20.5)	13.0(12.0,15.5)	5.518	<0.001
Recovery time (min)	6.0(5.0,7.5)	5.0(4.0,6.0)	2.617	0.009
HR reduction (beats/min)	3.0(3.0,3.0)	3.0(2.0,5.0)	0.701	0.483
SBP reduction (mmHg)	8.0(7.0,10.0)	6.0(3.0,9.5)	2.439	0.015
DBP reduction (mmHg)	5.0(4.0,6.5)	3.0(−0.5,7.0)	2.944	0.003

Notes: a, Chi-square test; b, independent-samples *t*-test. These comparisons are exploratory.

Table 7 Multivariable Logistic Regression Analysis of Factors Associated with Hiccups

Variable	B	SE	Wald	P	OR	*95% CI for OR*	
						Lower	Upper
Remimazolam (0.3mg kg^{-1})	−0.978	0.386	6.440	0.011	0.376	0.177	0.800
Injection rate (10s)	−1.428	0.380	14.123	<0.001	0.240	0.114	0.505
Age (years)	−0.022	0.017	1.710	0.191	0.978	0.946	1.011
Sex (Male)	0.760	0.488	2.427	0.119	2.139	0.822	5.567
BMI	0.112	0.098	1.306	0.253	1.119	0.923	1.356
Smoking	0.585	0.535	1.198	0.274	1.796	0.630	5.123
Hypertension	0.343	0.497	0.475	0.491	1.409	0.532	3.730
Diabetes	−0.858	0.857	1.002	0.317	0.424	0.079	2.276

Abbreviations: B, unstandardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index.

higher-dose regimen was also associated with less body movement and fewer supplemental boluses, indicating more complete and stable sedation, without evidence of additional haemodynamic compromise. We detected no significant interaction between dose and injection duration, suggesting that these two strategies can be combined without offsetting one another.

The selected dose levels and injection durations were determined based on a combination of prior literature, clinical feasibility, and our own pilot observations. Published trials of remimazolam for sedation during gastrointestinal endoscopy have used induction doses ranging from approximately 0.15 mg kg^{-1} in elderly outpatients undergoing colonoscopy[23] to 0.20–0.25 mg kg^{-1} in adult colonoscopy,[24] with Phase II dose-ranging work supporting the broader applicability of remimazolam in endoscopic sedation;[25] doses of 0.20–0.30 mg kg^{-1} have additionally been used as induction regimens in non-endoscopic procedural settings.[26] We selected 0.3 and 0.4 mg kg^{-1} to span a clinically

meaningful contrast between a moderate and a relatively high single induction dose, consistent with the upper end of current clinical practice in our centre and intended to provide more complete sedation while minimizing the need for rescue boluses. In our pilot observation, the incidence of hiccups appeared to differ between these two dose levels, which supported their selection as the two factor levels in the 2×2 factorial design. The injection durations of 10s and 20s were chosen to represent two practical bolus-administration strategies routinely employed during painless colonoscopy: a rapid injection at the shorter end of clinical practice, and a slower injection that remains readily standardizable in routine workflow without prolonging the induction phase. This design therefore enabled us to examine whether both the total remimazolam dose and the rate of bolus delivery contributed independently to hiccup risk.

Hiccups are generally considered a myoclonic-like phenomenon mediated by a brainstem reflex arc.[12] Pathophysiologically, this reflex arc comprises afferent fibres that transmit sensory input from somatic and visceral structures to central brainstem centres, motor fibres innervating the diaphragm, and accessory neural pathways supplying the intercostal muscles.[9,13,14] GABAergic signalling may be implicated in the pathophysiology of hiccups, and hiccup generation may also involve serotonergic pathways and drug exposure.[9]

One possible explanation for the higher incidence of hiccups with the 0.3 mg kg^{-1} regimen is that this dose may fall within an intermediate range in which central nervous system inhibition is initiated but suppression of subcortical excitatory drive remains incomplete. In such a state, reflex circuits involved in hiccup generation may remain relatively hyperexcitable. Although direct mechanistic evidence remains limited, this interpretation is broadly consistent with recent reports linking remimazolam to hiccups and paradoxical neurobehavioural responses,[10,15] as well as with emerging evidence that ultra-short-acting benzodiazepines may exert non-uniform effects across GABAA-dependent neural circuits.[27]

Our secondary outcome data provide additional support for this interpretation. Patients receiving 0.4 mg kg^{-1} not only experienced fewer hiccups, but also showed less body movement and required fewer supplemental boluses, together indicating more complete and stable sedation at this dose. As remimazolam exerts its sedative effects through GABAA receptors,[8] a plausible explanation is that the higher-dose regimen more effectively suppressed reflex-related excitatory pathways involved in hiccup generation.[8,9] In this context, deeper and more stable GABAergic sedation may have reduced the likelihood that brainstem reflex circuits, including vagal–phrenic components, remained sufficiently excitable to precipitate hiccups.[9]

We also found that a slower bolus injection rate (20s) significantly reduced the overall incidence of hiccups, yet was associated with a longer duration of hiccup episodes when they did occur. A pharmacokinetic–pharmacodynamic explanation may account for this seemingly paradoxical finding. A rapid bolus injection over 10s may produce a steeper early rise in plasma and effect-site remimazolam concentrations, resulting in a transiently higher peak exposure to the central nervous system.[8,20] By contrast, slower administration over 20s is likely to attenuate this early peak and smooth the concentration–time profile, thereby reducing the likelihood of activating hiccup-related brainstem reflex circuitry.[8,20–22]

However, in highly susceptible individuals, a more gradual rise in concentration may also prolong the time spent within an intermediate concentration range in which reflex excitability is not fully suppressed, potentially allowing hiccup episodes to persist for longer once triggered. By contrast, rapid bolus administration may be more likely to provoke hiccups initially because of the sharper early CNS exposure, but may also carry patients more quickly beyond this putative excitability window into deeper sedation, after which the episodes subside.[20,21] Although direct mechanistic evidence for such a threshold effect remains limited, this interpretation is consistent with contemporary pharmacokinetic and pharmacodynamic models of remimazolam and with emerging clinical observations linking remimazolam to hiccups.[10,11,20–22]

In routine painless colonoscopy, both procedural efficiency and patient safety are clinically important. Our findings suggest that remimazolam 0.4 mg kg^{-1} administered as a slow bolus over 20s may represent a clinically feasible regimen offering a favourable balance among hiccup prevention, operating conditions, and haemodynamic stability. From a broader clinical perspective, hiccups during sedated endoscopy are not merely a nuisance: repetitive diaphragmatic and abdominal contractions can provoke involuntary patient movement, disrupt stable scope manipulation, interrupt the continuity of inspection or therapeutic procedures, and necessitate rescue sedative boluses. Such interruptions may, in

turn, prolong procedure time and increase the need for additional sedative administration, which may contribute to sedation-related adverse events including respiratory depression and haemodynamic instability.[28] Reducing hiccups is therefore relevant not only to anaesthesiologists and endoscopists, but also to endoscopy nurses, day-surgery administrators, and most importantly to patients, whose comfort and recovery experience may also be affected.[29] Although hiccups are not generally regarded as a major complication, their cumulative impact on procedural quality should not be underestimated, particularly in high-volume endoscopy settings.

Limitations

This study has several limitations. First, as a single-centre trial that excluded older patients (>65 years) and high-risk individuals (ASA physical status IV–V), its generalizability to broader clinical populations remains uncertain. Second, although the baseline age imbalance was accounted for in the primary multivariable analysis, future studies incorporating age-stratified randomization would be needed to more fully exclude residual confounding. Third, multiple secondary and subgroup comparisons were performed and should therefore be regarded as exploratory, particularly because some non-normally distributed secondary endpoints were analysed using non-parametric methods without covariate adjustment. Fourth, the sample size calculation was based on pilot data in which the incidence of hiccups with 0.4 mg kg^{-1} was less than 5%, whereas the observed incidence in this trial was 25.6%. This discrepancy may reflect differences in patient characteristics, sample size of the pilot cohort, or injection technique, and suggests that the study may have been underpowered to detect smaller between-group differences. Finally, direct mechanistic evidence linking remimazolam pharmacokinetics to hiccup generation remains limited, and the proposed threshold-window explanation should be considered hypothesis-generating rather than definitive.

Conclusion

In this 2×2 factorial randomized trial, both a higher remimazolam dose (0.4 mg kg−1) and a slower bolus injection rate (20 s) were independently associated with a lower incidence of hiccups during painless colonoscopy. Together, these findings suggest that remimazolam 0.4 mg kg−1 administered over 20s may offer the most favourable balance between hiccup prevention, procedural conditions and haemodynamic stability in this study population.

Data Sharing Statement

The deidentified individual participant data and study materials used during the current study, including the study protocol and statistical analysis plan, will be available from the corresponding author upon reasonable request, beginning from the date of publication and for a period of 5 years.

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Disclosure

The authors declare that they have no competing interests in this work.

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