



# Efficacy and safety of different doses of remimazolam tosylate for colonoscopy: single-center, prospective, randomized, double-blind, parallel trial

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**Background:** Remimazolam tosylate is a new sedative combining the advantages of etomidate with remifentanyl. Remimazolam tosylate shows effective in colonoscopy, but the optimal dose is not confirm. In this study, a single-center, prospective, randomized, double-blind, parallel trial were performed to compare the efficacy and safety of different doses of remimazolam tosylate for colonoscopy.

**Methods:** Before colonoscopy, 120 recruited patients were randomized with a 1:1:1 ratio into 3 treatment groups: group A, 0.1 mg/kg remimazolam tosylate; group B, 0.15 mg/kg remimazolam tosylate; group C, 0.2 mg/kg remimazolam tosylate. Patients received 1 µg/kg fentanyl by intravenous injection over 30 s followed by the respective induction dose of remimazolam tosylate over 1 min ( $\pm 5$  s). When adequate sedation was achieved, colonoscopy was performed. Sedation was maintained at Modified Observer's Assessment of Alertness/Sedation (MOAA/S)  $\leq 4$  during the procedure. The additional administration of remimazolam tosylate (0.05 mg/kg per time) was permitted when necessary.

**Results:** Forty-one patients, 39 patients and 40 patients were respectively analyzed in group A, group B and group C. The procedural success rate was 80.49%, 87.18% and 95.00% in group A, group B and group C, respectively. During the induction period, patients in group A required additional doses of remimazolam tosylate more frequently than in group B and group C, but less during the maintenance period (all  $P < 0.05$ ). There was no significant difference in the induction time or time to recovery among the three groups. Incidence of adverse events (such as hypotension, hypoxemia and bucking) was similar among the three groups.

**Conclusions:** The initial loading doses of 0.1, 0.15, and 0.2 mg/kg remimazolam tosylate were all efficacy and safety for patients undergoing colonoscopy, and fewer times of the drug was re-administered.

**Trial Registration:** Chinese Clinical Trial Registry ChiCTR2000041331

**Keywords:** Benzodiazepines; colonoscopy; efficacy; remimazolam tosylate; safety

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## Introduction

Colonoscopy is an important technique for the diagnosis and treatment of colon-related diseases (1,2), but patients can find it uncomfortable and/or distressing without sedation, which is a drug-induced depression of consciousness. The clinical objectives of administering sedatives for gastrointestinal endoscopy are to relieve patient anxiety and discomfort, improve the outcome of the examination, and diminish the patient's memory of the event (3). The selection of drug is based on the type of endoscope, and the patient's condition, with the premise of ensuring the patient safety and the quality of sedation. Although the current anesthesia protocols can basically meet the sedation needs of ambulate surgery, there are some safety issues that should not be ignored, especially for the growing elderly population.

As a traditional sedative, benzodiazepines have little effect on circulation, but sedation is inadequate, and metabolites are still active, thus significantly prolonging the patient's waking time (4). Propofol, currently the most widely used sedative, has a high success rate, but often results in deep sedation (5), leading to circulatory depression, for which there is no specific reversal agent. In a retrospective study of 73,029 patients undergoing gastrointestinal endoscopy, patients administered propofol had a higher incidence of cardiac arrest and death compared with those using midazolam-fentanyl (8.07/10,000 *vs.* 4.28/10,000 *vs.* 0.67/10,000 *vs.* 0.44/10,000, respectively), of which 72% was related to airway management difficulties. Approximately 90% of cardiac arrests occur in patients administered propofol (6).

Remimazolam tosylate is a new sedative combining the advantages of etomidate with remifentanyl. *In vivo*, remimazolam is rapidly hydrolyzed to zolam propionic acid by a nonspecific esterase, and zolam propionic acid has only 1/400 of the affinity for GABAA receptor (7). Theoretically, remimazolam tosylate has the characteristics of fast metabolism and little influence on the circulation. *In vivo* studies report that 0.37–2.21 mg/kg of remimazolam has quick onset and recovery without cardiorespiratory depression (8,9). Remimazolam tosylate had been used in the induction and maintenance of general anesthesia (10,11). For patients undergoing upper gastrointestinal endoscopy, the sedation efficiency of 0.15 and 0.2 mg/kg remimazolam tosylate was significantly better than patients with 0.075 mg/kg midazolam. Meanwhile, remimazolam tosylate had shorter onset time and recovery time than midazolam (12). One previous study has reported that under the supervision of endoscopists, remimazolam can be administered safely for outpatient colonoscopy, and it allows faster recovery of neuropsychiatric function compared with midazolam (13). Further, Rex *et al.* have reported remimazolam is safe and efficient in procedural sedation of high risk American Society of Anesthesiologists (ASA) patients undergoing colonoscopy, with the doses of remimazolam 1.25–2.5 mg (14).

It has reported remimazolam tosylate at 0.1, 0.15, and 0.2 mg/kg (off-label dose) is safe and effective for gastroscopy. At present, remimazolam tosylate has also been shown to be effective in colonoscopy. The dosage of remimazolam tosylate used in many studies was the instruction dose (13–15), but off-label dose is often needed in practical application. In this study, we compared the efficacy and safety of the three doses of remimazolam tosylate for colonoscopy, which might provide better guide in clinical use and improve the comfort for patients. We present the following article in accordance with the CONSORT reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5133/rc>).

## Methods

### Study design

This single-center, prospective, randomized, double-blind, parallel trial was performed from November 2020 to October 2021 at The First Affiliated Hospital of Suzhou University, assessing the efficacy and safety of remimazolam tosylate in different doses for colonoscopy. The study was conducted in accordance with the Declaration of Helsinki

### Highlight box

#### Key findings

- The initial loading doses of 0.1, 0.15, and 0.2 mg/kg remimazolam tosylate were efficacy and safety for patients undergoing colonoscopy.

#### What is known and what is new?

- Off-label dose of remimazolam tosylate is often needed in practical application.
- We compared the efficacy and safety of the three doses of remimazolam tosylate for colonoscopy.

#### What is the implication, and what should change now?

- The trial drug's efficacy and appropriate dosage in different clinical settings are still needed to furtherly confirm.

(as revised in 2013). Before patient enrolment, this study was approved by the Institutional Review Board of The First Affiliated Hospital of Suzhou University (IRB No. 2020-165-1), and informed consent was taken from all the patients.

### ***Inclusion and exclusion criteria***

The inclusion criteria of the study were: (I) patients aged between 18 and 65 years; (II) with ASA physical status I–II; (III) body mass index (BMI) of 18–30 kg/m<sup>2</sup>; (IV) who were scheduled to undergo colonoscopy with sedation anesthesia; (V) participation had to be voluntary, written informed consent given and be willing to comply with study requirements. The operation time of colonoscopy is expected to be <30 min. The exclusion criteria included: (I) required complex endoscopic procedures (e.g., cholangiopancreatography, endoscopic ultrasonography, endoscopic mucosal resection, endoscopic submucosal dissection, transoral endoscopic submucosal dissection, transoral endoscopic myotomy, etc.); (II) requiring endotracheal intubation or laryngeal mask; (III) any heart disease, such as unstable angina pectoris, myocardial infarction, heart rate <50 beats/min, grade III atrioventricular block, severe arrhythmia, and others; (IV) severe respiratory disease; (V) psychiatric disorders, history of psychotropic drugs usage, and cognitive deficit; (VI) difficult respiratory management (grade IV Modified Mallampati score); (VII) uncontrolled blood pressure; (VIII) allergy or contraindication to benzodiazepines, opioids, propofol and their components; (IX) pregnant or breastfeeding; (X) enter into clinical trial within the past 3 months.

### ***Randomization and blinding***

Before colonoscopy, enrolled patients were randomized with a 1:1:1 ratio into the different doses of remimazolam tosylate groups using an online randomization tool. Remimazolam tosylate was diluted with normal saline to 36 mL (i.e., 1 mg/mL). In order to blind the patients, anesthesiologists, operators, and other medical staff, all study drugs were packaged in identical opaque, sealed envelopes.

### ***Study procedures and drug administration***

After routine bowel preparation, 120 enrolled patients were randomly assigned to 1 of the 3 treatment groups: an induction dose of remimazolam tosylate (Jiangsu

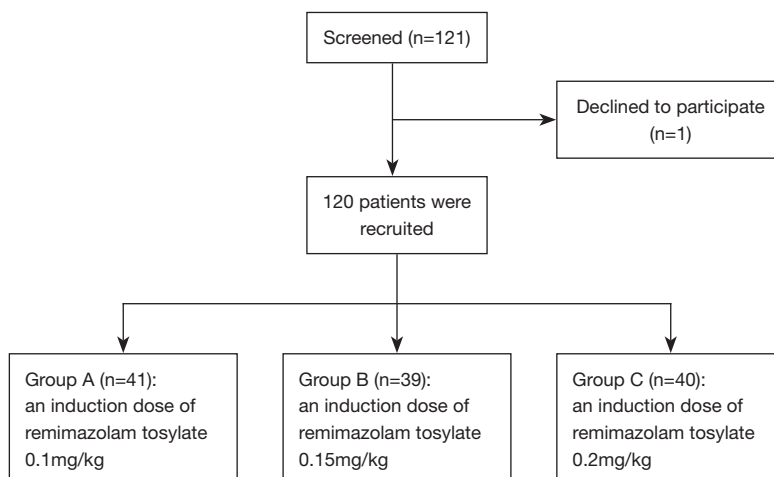
Hengrui Pharmaceutical Co. Ltd., China, 200413AK) 0.1 mg/kg (group A), 0.15 mg/kg (group B), or 0.2 mg/kg (group C). In the examination room, standard monitoring included electrocardiography, noninvasive cuff BP and pulse oximetry. Supplemental oxygen at 4 L/min was administered by nasal cannula.

Patients received 1 µg/kg fentanyl by intravenous injection over 30 s followed by the respective induction dose of remimazolam tosylate over 1 min (±5 s). Colonoscopy was initiated when adequate sedation [Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≤3] was achieved. At 1 min after the initial dose of remimazolam tosylate, another 0.05 mg/kg was administered if sedation was deemed to be inadequate (MOAA/S >3 or MOAA/S score ≤3 but colonoscopy failed).

Sedation was maintained at MOAA/S ≤4 during the procedure, with additional administration of remimazolam tosylate (0.05 mg/kg per time) permitted when necessary. If the supplemental bolus were not sufficient to obtain or maintain adequate sedation within a 15-min window, propofol was administered as rescue sedative medication for completion of colonoscopy. After the administration of remimazolam tosylate, sedation was assessed every minute until the patient was fully alert (3 consecutive MOAA/S scores of 5).

### ***Outcomes and definitions***

The primary outcome was the procedural success rate, which was assessed by the following conditions: (I) completion of the colonoscopy; (II) <3 additional administrations of remimazolam tosylate during the induction; (III) no requirement for rescue sedative; and (IV) no requirement for >5 top-ups of remimazolam tosylate within any 15-min period, or number of additional administrations (remimazolam tosylate) during colonoscopy. Secondary outcomes included: (I) procedural time; (II) the induction time of sedation, defined as the time from the initial dose to obtaining adequate sedation (the first MOAA/S ≤3); (III) time to fully alert, defined as the time interval from the ceasing administration of drugs to the first of three consecutive MOAA/S scores of 5; and (IV) the satisfaction of the patient, gastroenterologist and anesthetist. The safety outcomes were analyzed according to the incidence of adverse events, including following: (I) hypotension requiring treatment: defined as ≥20% in systolic blood pressure (SBP) from the pre-sedation value, or SBP ≤80 mmHg during the procedure from



**Figure 1** Study flow chart.

initial administration of the trial drug to fully alert; (II) incidence of hypoxemia: oxygen saturation <90% in the time from initial administration of trial drug to fully alert; (III) patient's recall of the colonoscopy as assessed by the Brice questionnaire after becoming fully alert; (IV) the incidence of bucking, nausea or vomiting during the colonoscopy; (V) the incidence of post procedural delirium by Mini-Mental State Examination (MMSE) scale.

### Statistical analysis

All statistical analyses were programmed and calculated by RStudio statistical analysis software. All tests were two-sided.  $P < 0.05$  was considered statistically significant, and the confidence interval was 95%. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range, IQR), and qualitative data are presented as numbers and frequencies. Data were analyzed using Kruskal-Wallis H test, Chi-squared test, or Fisher exact test, as appropriate.

## Results

### Patients' characteristics

From November 2020 to October 2021, a total of 121 patients willing to undergo colonoscopy were screened for eligibility; one declined to participate. The remaining 120 patients completed this study (Figure 1).

Patients' demographics and baseline characteristics are

shown in Table 1. The mean age was 45.58 years in group A, 45.28 years in group B and 45.25 years in group C. There were 65.9%, 43.6% and 65.0% males in group A, in group B, and group C respectively. BMI was similar among groups at 23.76, 23.79 and 24.13  $\text{kg}/\text{m}^2$  respectively. All patients were healthy and in ASA status I–II. There was 1 patient (2.44%) with a history of intestinal polyps in group A, and in group C there was 1 patient (2.50%) with a history of intestinal polyps, 1 (2.50%) with a history of hypertension and 1 (2.50%) with a history of anemia.

### Primary outcome

All patients in the three groups completed colonoscopy. The procedural success rate was 80.49% in group A, 87.18% in group B and 95.00% in group C. Fisher's exact test showed no statistically significant differences among the three groups ( $P = 0.142$ , Table 2). The number of additional administrations of remimazolam tosylate was 4 in group A, 2 in group B and 1 in group C, which was statistically significant ( $P < 0.01$ ). During the induction period, the frequency of adding remimazolam tosylate in group A was higher than in group B and group C ( $P < 0.05$ ). During the maintenance period, with increasing dosage, the number of additional doses decreased ( $P < 0.05$ ). The higher the initial dose, the less times remimazolam tosylate was topped up ( $P < 0.05$ ) (Table 2).

### Secondary outcomes

There was no significant difference among groups for

**Table 1** Baseline characteristics of patients undergoing colonoscopy

| Variables                               | Group A (n=41)    | Group B (n=39)    | Group C (n=40)    | P value |
|---|-------------------|-------------------|-------------------|---------|
| Demographics                            |                   |                   |                   |         |
| Age (years), mean $\pm$ SD              | 45.58 $\pm$ 13.13 | 45.28 $\pm$ 11.39 | 45.25 $\pm$ 11.36 | 0.991   |
| Female sex, n (%)                       | 14 (34.15)        | 22 (56.41)        | 14 (35.00)        | 0.075   |
| BMI (kg/m <sup>2</sup> ), mean $\pm$ SD | 23.76 $\pm$ 2.54  | 23.79 $\pm$ 3.11  | 24.13 $\pm$ 3.25  | 0.828   |
| Comorbidities, n (%)                    |                   |                   |                   |         |
| Hypertension                            | 0                 | 0                 | 1 (2.50)          | 0.525   |
| Intestinal polyps                       | 1 (2.44)          | 0                 | 1 (2.50)          |         |
| Diabetes                                | 0                 | 0                 | 0                 |         |
| Coronary heart disease                  | 0                 | 0                 | 0                 |         |
| Anemia                                  | 0                 | 0                 | 1 (2.50)          |         |
| Operation history, n (%)                |                   |                   |                   |         |
| No                                      | 39 (95.12)        | 38 (97.44)        | 38 (95.00)        | 0.445   |
| Yes                                     | 2 (4.88)          | 0                 | 1 (2.50)          |         |

SD, standard deviation; BMI, body mass index. Group A, 0.1 mg/kg remimazolam tosylate; Group B, 0.15 mg/kg remimazolam tosylate; Group C, 0.2 mg/kg remimazolam tosylate.

**Table 2** Procedural success of colonoscopy

| Variables   | Group A (n=41) | Group B (n=39) | Group C (n=40) | P value |
|---|----------------|----------------|----------------|---------|
| Procedure success, n (%)  | 33 (80.49)     | 34 (87.18)     | 38 (95.00)     | 0.142   |
| No. of additional doses of remimazolam tosylate, median [range] | 4 [2, 4]       | 2 [1, 3]       | 1 [0, 3]       | <0.01   |
| Induction, median [range]                                       | 1 [0, 1]       | 0 [0, 0]       | 0 [0, 0]       | <0.01   |
| Maintenance, median [range]                                     | 2 [1, 4]       | 1 [1, 3]       | 1 [0, 2.25]    | 0.022   |

Group A, 0.1 mg/kg remimazolam tosylate; Group B, 0.15 mg/kg remimazolam tosylate; Group C, 0.2 mg/kg remimazolam tosylate.

**Table 3** Secondary outcomes of colonoscopy

| Variables   | Group A (n=41)      | Group B (n=39)               | Group C (n=40)               | P value |
|---|---------------------|------------------------------|------------------------------|---------|
| Procedural duration (min), median [range]         | 11.93 [9.18, 25.07] | 10.18 [8.06, 15.39]          | 12.00 [9.02, 17.79]          | 0.285   |
| Induction time of sedation (min), median [range]  | 4.51 [3.65, 5.93]   | 4.22 [3.13, 5.69]            | 4.94 [4.14, 6.23]            | 0.206   |
| Satisfaction of patient, mean $\pm$ SD            | 9.04 $\pm$ 0.54     | 9.11 $\pm$ 0.59              | 9.12 $\pm$ 0.52              | 0.732   |
| Satisfaction of gastroenterologist, mean $\pm$ SD | 8.82 $\pm$ 0.63     | 9.15 $\pm$ 0.56 <sup>a</sup> | 9.17 $\pm$ 0.50 <sup>a</sup> | 0.009   |
| Satisfaction of anesthesiologist, mean $\pm$ SD   | 8.70 $\pm$ 0.68     | 9.09 $\pm$ 0.61 <sup>a</sup> | 9.21 $\pm$ 0.50 <sup>a</sup> | 0.001   |

Group A, 0.1 mg/kg remimazolam tosylate; Group B, 0.15 mg/kg remimazolam tosylate; Group C, 0.2 mg/kg remimazolam tosylate. Range (min, max); <sup>a</sup>, P<0.05, vs. group A. SD, standard deviation.

procedural time (*Table 3*). Induction time of sedation and the time to fully alert were similar among the groups (P>0.05). There was no significant difference in the satisfaction of

the patients in the three groups (P=0.732, *Table 3*), but the satisfaction of gastroenterologists and anesthesiologists were significantly lower for group A than for groups B and C (all

**Table 4** Adverse events

| Variables                 | Group A (n=41) | Group B (n=39) | Group C (n=40) | P value |
|---------------------------|----------------|----------------|----------------|---------|
| Hypotension, n (%)        | 1 (2.44)       | 1 (2.56)       | 0              | 0.601   |
| Hyoxemia, n (%)           | 0              | 1 (2.56)       | 0              | 0.351   |
| Procedure recall, n (%)   | 2 (4.88)       | 0 (0.00)       | 0 (0.00)       | 0.141   |
| Bucking, n (%)            | 2 (4.88)       | 3 (7.69)       | 2 (5.00)       | 0.569   |
| Nausea or vomiting, n (%) | 0              | 0              | 0              |         |
| Delirium, n (%)           | 0              | 0              | 0              |         |

Group A, 0.1 mg/kg remimazolam tosylate; Group B, 0.15 mg/kg remimazolam tosylate; Group C, 0.2 mg/kg remimazolam tosylate.

$P < 0.05$ ). Adverse events (i.e., hypotension, hyoxemia and bucking) were similar among the three groups (all  $P > 0.05$ , Table 4). None of the patients had nausea or vomiting, or delirium, and two patients in the group A could recall the procedure.

## Discussion

Remimazolam is a new ultra-short-acting benzodiazepine that acts on the  $\gamma$ -aminobutyric acid (GABA) receptor (16). In contrast to other benzodiazepines, it has high clearance, small volume of distribution, inactive carboxylic acid metabolite, and improved controllability. This study was designed to evaluate its efficacy and safety at different doses for colonoscopy, and we found that (I) the different doses of remimazolam tosylate had the same potency in the efficiency analysis; (II) the higher the initial dose, the better the success rate and the fewer times remimazolam tosylate was topped up; and (III) no statistically significant differences in the incidence of adverse events among the different dose groups in the safety analysis.

The success of the colonoscopy was 80.5%, 87.2%, and 95% in the 0.1, 0.15 and 0.2 mg/kg groups respectively. Our results differed from those of a previous study (12), probably because we used only a single dose of remimazolam and in combination with fentanyl. Enhanced recovery protocols use one or more approaches to improve a procedure's clinical outcome. For colonoscopies, this might involve combining several agents with different mechanisms of action to achieve the desired level of anesthesia (17,18). Intravenous fentanyl can provide analgesia and sedation, reducing the dose of sedative used and significantly shortening the recovery time (19). Without fentanyl, the single dose of remimazolam was able to induce sedation, with a success rate of 32%, 56%, and 64% in the 0.10, 0.15,

and 0.20 mg/kg groups respectively (12). With fentanyl, the procedural success of remimazolam was 91.3% (13), similar to our findings. Our study showed that an initial loading dose from 0.1 to 0.2 mg/kg remimazolam tosylate were effective sedation for colonoscopy. Importantly, the higher the initial dose, the less times remimazolam tosylate needed topping up, but the recovery time was not prolonged. The pharmacokinetics of remimazolam are linear, and the time-dose correlation half-life of remimazolam was not affected by infusion time. Our results also confirmed that there was no significant difference in the time to recovery for the different doses of remimazolam tosylate. Similarly, Pambianco *et al.* found that the patients in remimazolam group had the most rapid recovery of neuropsychiatric function, readiness for discharge, and return to feeling completely normal consistent with previous data (20).

One important concern regarding endoscopic sedation is sedation-related complications, which can lead to significant morbidity and occasionally the death of patients. Theoretically, cardiovascular and respiratory depression is associated with moderate and deep sedation (21). Our safety results showed no significant difference in the incidence of sedative hypotension, hypoxemia, hyperhidrosis and hiccups among the groups with different doses of remimazolam tosylate. The three groups in our study maybe had different sedation levels, but we speculate that they were above moderate sedation. Our study results also suggested that remimazolam tosylate had mild effects on the circulatory and respiratory systems. Therefore, 0.1, 0.15 and 0.2 mg/kg remimazolam tosylate have an acceptable safety and tolerability profile, without severe adverse events. Rex *et al.* also demonstrated that remimazolam can be safely administered under the guidance of an endoscopist during outpatient colonoscopy (14). There are also studies of the use of remimazolam in general anesthesia, and the results all

confirm that it is safe and effective, and that the dosage of vasopressors used during surgery is significantly reduced (11).

## Conclusions

In conclusion, the initial loading doses of 0.1, 0.15, and 0.2 mg/kg remimazolam tosylate were efficacy and safety for patients undergoing colonoscopy, and the fewer times of the drug was re-administered. Remimazolam tosylate in the range of 0.1–0.2 mg/kg allows rapid recovery from sedation and has less potential to cause cardiovascular and respiratory depression; adverse effects did not increase with increasing dose.

Our study had several limitations. First, the sample size of this trial was relatively small, and the results may not be representative. Second, observation indicators were inadequate, such as the evaluation by operators and patients in the three groups. Further studies are still needed to confirm the trial drug's efficacy and appropriate dosage in different clinical settings.

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## Footnote

*Reporting Checklist:* The authors have completed the CONSORT reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5133/rc>

*Trial Protocol:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5133/tp>

*Data Sharing Statement:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5133/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5133/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). Before patient enrolment, this study was approved by the Institutional Review Board of The First Affiliated Hospital of Suzhou University (IRB No. 2020-165-1), and informed consent was taken from all the patients.

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## References

1. Nagata N, Ishii N, Manabe N, et al. Guidelines for Colonic Diverticular Bleeding and Colonic Diverticulitis: Japan Gastroenterological Association. *Digestion* 2019;99 Suppl 1:1-26.
2. Watanabe J, Ikegami Y, Tsuda A, et al. Lidocaine spray versus viscous lidocaine solution for pharyngeal local anesthesia in upper gastrointestinal endoscopy: Systematic review and meta-analysis. *Dig Endosc* 2021;33:538-48.
3. ASGE Standards of Practice Committee; Early DS, Lightdale JR, et al. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2018;87:327-37.
4. Ruesch D, Neumann E, Wulf H, et al. An allosteric coagonist model for propofol effects on  $\alpha 1\beta 2\gamma 2L$   $\gamma$ -aminobutyric acid type A receptors. *Anesthesiology* 2012;116:47-55.
5. Rex DK, Heuss LT, Walker JA, et al. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology* 2005;129:1384-91.
6. Tsai HC, Lin YC, Ko CL, et al. Propofol versus midazolam for upper gastrointestinal endoscopy in cirrhotic patients: a meta-analysis of randomized controlled trials. *PLoS One* 2015;10:e0117585.
7. Antonik LJ, Goldwater DR, Kilpatrick GJ, et al. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg* 2012;115:274-83.
8. Upton R, Martinez A, Grant C. A dose escalation study in sheep of the effects of the benzodiazepine CNS 7056 on

- sedation, the EEG and the respiratory and cardiovascular systems. *Br J Pharmacol* 2008;155:52-61.
9. Upton RN, Somogyi AA, Martinez AM, et al. Pharmacokinetics and pharmacodynamics of the short-acting sedative CNS 7056 in sheep. *Br J Anaesth* 2010;105:798-809.
  10. Wesolowski AM, Zaccagnino MP, Malapero RJ, et al. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. *Pharmacotherapy* 2016;36:1021-7.
  11. Wahler S. Difference in vasopressor use and usage patterns in patients undergoing cardiac surgery with remimazolam vs propofol/sevoflurane for general anesthesia. In: Conference: Anesthesiology 2015, San Diego.
  12. Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg* 2015;120:771-80.
  13. Rex DK, Bhandari R, Desta T, 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;88:427-437.e6.
  14. Rex DK, Bhandari R, Lorch DG, et al. Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. *Dig Liver Dis* 2021;53:94-101.
  15. 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;12:4594-603.
  16. Rogers WK, McDowell TS. Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. *IDrugs* 2010;13:929-37.
  17. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002;183:630-41.
  18. Lau CS, Chamberlain RS. Enhanced Recovery After Surgery Programs Improve Patient Outcomes and Recovery: A Meta-analysis. *World J Surg* 2017;41:899-913.
  19. Ulmer BJ, Hansen JJ, Overley CA, et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003;1:425-32.
  20. Pambianco DJ, Borkett KM, Riff DS, et al. A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2016;83:984-92.
  21. Amornytin S. Sedation-related complications in gastrointestinal endoscopy. *World J Gastrointest Endosc* 2013;5:527-33.

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