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A Comparison of Remimazolam versus Propofol on Blood Pressure Changes During Therapeutic Endoscopic Retrograde Cholangiopancreatography: A Randomized Controlled Trial

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BACKGROUND: Intraoperative hypotension is the most common adverse event in endoscopic retrograde cholangiopancreatography (ERCP) and is usually attributed to the vasodilatory effect of the anesthetic. The aim of this randomized controlled trial was to evaluate the impact of remimazolam versus propofol on blood pressure changes during the therapeutic ERCP procedure.
METHODS: Adult patients scheduled for elective therapeutic ERCP were randomized to receive either remimazolam or propofol anesthesia (40 patients in each group). The primary outcomes included the change in mean arterial pressure (MAP) during induction and the area under the baseline (AUB), calculated as the blood pressure below baseline multiplied by the duration, throughout the procedure. These measures, respectively, indicated the severity of blood pressure decrease during anesthesia induction and the overall impact of blood pressure changes throughout the procedure. Any incidences of hypotension, defined as MAP <65 mm Hg for at least 1 minute, were recorded. The recovery time and any adverse events were also reported.
RESULTS: The change in MAP after induction was smaller in the remimazolam group compared to the propofol group (−7.5 [−14.0 to 0] mm Hg vs −25.0 [−33.8 to −14.3] mm Hg), with a median difference of 17.0 mm Hg (95% confidence interval [CI], 12.0–22.0; P <.001). The AUB in the remimazolam group was less than in the propofol group (−373 [−82 to −854] mm Hg·min vs −705 [−272 to −1100] mm Hg·min), with a median difference of 255 mm Hg·min (95% CI, 29–477; P =.021). The incidence of hypotension was significantly lower for remimazolam than propofol (5% vs 30%; P =.006). There were no serious adverse events in either group.
CONCLUSIONS: Remimazolam may be considered as an alternative to propofol for general anesthesia during therapeutic ERCP procedures, with the potential advantage of stable hemodynamics. (Anesth Analg 2025;141:90–9)

KEY POINTS

- **Question:** Does remimazolam cause a smaller drop in blood pressure during induction and maintenance of general anesthesia for therapeutic endoscopic retrograde cholangiopancreatography (ERCP) than propofol?
- **Findings:** Remimazolam anesthesia resulted in a less of a drop in mean arterial pressure (MAP) after induction and a smaller cumulative decrease in MAP compared to propofol.
- **Meaning:** Reduced hypotension with remimazolam suggests it may have potential benefits for nonoperating room anesthesia including complex gastrointestinal endoscopic procedures.

Complex upper gastrointestinal endoscopy presents challenges for anesthesia.[1] The largest portion of nonoperating room malpractice claims involving anesthesiologists arises from complex endoscopy procedures, with endoscopic retrograde cholangiopancreatography (ERCP) being the leading contributor.[2] More than 1 million individuals worldwide undergo ERCP annually.[3]

Based on recent consensus statements, general anesthesia (GA) is preferred for therapeutic complex

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ERCP procedures.[4] A recent pro-con debate comparing the choice of GA or monitored anesthesia care (MAC) for ERCP pointed out the dilemma that GA afforded superior airway protection to MAC but carried an increased risk of hypotension.[5,6] Furthermore, most ERCP patients are elderly with chronic illnesses, suffering from malnutrition, weakness, and often obstructive jaundice and hypoalbuminemia. These issues, compounded by the procedure's prone/semiprone positioning, contributed to increased risks of hypotension.[7–9]

Intraoperative hypotension increases the risk of complications such as myocardial ischemia, kidney injury, acute delirium, and 30-day mortality.[10–13] In endoscopic procedures, anesthesia is commonly conducted using either inhaled or intravenous anesthetics, with propofol often serving as the primary intravenous choice.[1,14] Remimazolam is a new ultrashort-acting benzodiazepine receptor agonist, that may have hemodynamic advantages over propofol.[15,16] In comparison to propofol, remimazolam used as a GA reduced the incidence of hypotension in a variety of surgical procedures.[17–20] Thus, remimazolam administered as a GA for nonoperating room anesthesia may also have a reduced incidence of hypotension.

Thus, we conducted this randomized trial to test the hypothesis that remimazolam would result in less hypotension during anesthesia induction and throughout the ERCP procedure compared to propofol.

METHODS

Trial Design

The trial was a single-center randomized controlled study, conducted at the Second Xiangya Hospital, Central South University, China, from August 10, 2021, to August 31, 2022. This trial was approved by the Clinical Research Ethics Committee of our hospital (protocol no. 2021-079) and registered with the China Clinical Trial Registry (www.chictr.org.cn, ChiCTR2100049314, principal investigator: R.-P. Dai, date of registration: July 30, 2021). The trial protocol followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines, and written informed consent was obtained from all patients before their enrollment.

Patients

Adult patients (≥18 years old) with American Society of Anesthesiologists (ASA) physical status I to III scheduled for elective therapeutic ERCP procedure under GA were included. Exclusion criteria included emergency ERCP, uncontrolled hypertension (>160/100 mm Hg), severe cardiovascular disease, an anticipated difficult airway, morbid obesity, drug abuse, communication difficulties, recent respiratory infections, allergy, intolerance to general anesthetics, breast-feeding or pregnant women, and participation in other clinical studies within the previous 3 months.

Randomization and Blinding

Patients were randomly assigned to receive remimazolam or propofol for anesthesia at a 1:1 allocation ratio by a computer-generated randomization sequence (simple randomization) using SPSS software (ver. 25.0, IBM). Because the trial drugs can be easily distinguished from the external appearance of their formulations, researchers in this study consisted of administration researchers (unblinded) and management researchers (blinded). The unblinded researchers accomplished the drug dispensing, transfer, and administration, but did not participate in other trial procedures such as screening, outcome assessment, data collection, or analysis.

Specifically, the prepared trial medicines in opaque syringes were brought into the endoscopic room by an unblinded researcher. A dark curtain was hung on the side of the punctured forearm of patients, to separate the blinded and unblinded researchers. Behind the curtain, the unblinded researcher managed the infusion and pump equipment under the covered opaque sheets, following the voice instructions from the blinded researchers on the other side of the curtain. For voice commands involving the trial drugs (remimazolam/propofol), "sedative medication" uniformly represented the drug names, with dosage expressed as "upregulate/downregulate pumping by one/several levels" or "administer one/several intravenous bolus doses." When the drug infusion was terminated at the end of the procedure, the unblinded researcher removed all the covered infusion equipment and left the room immediately.

Anesthesia Management

All patients received a standard intravenous fluid administration. Heart rate (HR), electrocardiogram (ECG), end-tidal CO_2, and pulse oxygen saturation (Spo_2) were recorded every 5 minutes. Given the prolonged duration of therapeutic ERCP procedures (typically taking ≥30 minutes), the prevalent weakness existing in patients, and the challenges of accurately monitoring blood pressure with arm cuffs in the semiprone position, radial artery cannulation for continuous monitoring was adopted as standard practice in our hospital. Processed electroencephalography was continuously monitored throughout each procedure (bispectral index [BIS] VT21404, Medtronic).

For induction, patients in the remimazolam group were given a bolus of remimazolam (Yichang Renfu Pharmaceutical Co., Ltd) 0.2 mg/kg, while patients in the propofol group were induced with propofol

(AstraZeneca plc.) 1.5 mg/kg. Sedative induction was completed by pump-controlled infusion in 1 minute ±5 seconds, immediately followed by infusion of remifentanil (Yichang Renfu Pharmaceutical Co., Ltd) 2 ug/kg in 30 seconds, as the induction drugs used all had a rapid onset of action. The induction success required 2 outcomes: (1) loss of responsiveness defined as a loss of response to a shoulder shake; (2) BIS <60.[21] A bolus of 0.05 mg/kg remimazolam or 0.5 mg/kg propofol was given repeatedly every 1 minute as supplemental doses if induction success did not occur 2 minutes after the initial dose. After administering up to 3 supplemental doses without achieving successful induction, researchers could declare induction failure and switch to any alternative sedation. When anesthesia induction was successful, an endoscopic supraglottic airway (endoscopic laryngeal mask airway, specifically designed for endoscopy, from Zhejiang Jiancheng Medical Technology Co., Ltd.) was placed. A schematic of the endoscopic laryngeal mask airway is shown in Supplemental Digital Content 1, Supplementary Figure S1, http://links.lww.com/AA/F101.

A continuous infusion of remimazolam (0.8 mg/kg/h) or propofol (4 mg/kg/h) was immediately started after the induction bolus; simultaneously remifentanil was infused at an initial rate of 0.15 μg/kg/min. Intraoperative BIS values were maintained between 40 and 60 by modifying the infusion rate of remimazolam (0.5–2.0 mg/kg/h) or propofol (2–8 mg/kg/h) according to the following rules: when the BIS exceeded 60, the infusion rates of remimazolam (or propofol) and remifentanil were escalated by 1 level, with increments of 0.2 mg/kg/h for remimazolam, 1 mg/kg/h for propofol, and 0.01 μg/kg/min for remifentanil. Conversely, when the BIS fell <40, the infusion rates of remimazolam (or propofol) and remifentanil were downregulated by 1 level at the same aforementioned rates. When a body movement was observed, a bolus of 5 mg remimazolam (or 50 mg propofol) in combination with remifentanil 25μg was administered intravenously. Reassessment was performed 3 minutes after each adjustment, and the above maneuvers could be repeated until the BIS was maintained at 40 to 60 and the patient's body movements ceased.

Patients were kept in a semiprone position (right body up at 30 degrees) during the procedure. All ERCP procedures were performed by 1 of 2 experienced endoscopists. Abnormal hemodynamics was treated based on the following criteria: intravenous administration of 0.2 mg metaraminol for MAP <65 mm Hg; 10 mg urapidil for MAP >110 mm Hg; 0.25 mg atropine for HR <50/min; and 10 mg esmolol for HR >120/min.

The infusion of all anesthetics was discontinued when the endoscopist retracted the probe outward of the duodenum. Then a bolus of 0.3 mg flumazenil (Nhwa Pharmaceutical Co., Ltd) was administered as an antagonist for remimazolam, or an equal volume of saline was given to the propofol group, when the probe left the oral cavity. The attending anesthesiologist determined when to remove the laryngeal mask airway and evaluate the recovery of patients in the postanesthesia care unit (PACU). Patients were transferred to the ward when the modified Aldrete Score was≥9 points.[22] Intraoperative awareness was assessed using the Brice Questionnaire before the patient left the PACU.[21]

Outcomes

The primary outcomes were the change in MAP from baseline during anesthesia induction and the area under baseline MAP (area under the baseline [AUB]) throughout the procedure.

The baseline value of MAP was recorded when patients had sufficient rest after arterial puncture (at least 5 minutes). The duration of induction was defined as the time from the initiation of the sedative infusion to the time of induction success. Success was defined as the achievement of both loss of responsiveness and a BIS score <60. AUB was determined by calculating the difference between MAP and the baseline MAP, multiplied by the time in minutes when MAP was below the baseline. A schematic illustrating the change in MAP during induction and the AUB calculation throughout the ERCP procedure is presented in Figure 1.

Secondary outcomes included the following: the time-weighted average of MAP < baseline was corrected for the duration of anesthesia, defined as the AUB divided by the duration of anesthesia,[23] the number of hypotensive events (defined as MAP <65 mm Hg for at least 1 minute),[23] duration of hypotension, the lowest MAP throughout the procedure, and the requirement for metaraminol. The number of hypertension events (defined as MAP >110 mm Hg), tachycardia (defined as HR > 120/min), bradycardia (defined as HR < 50/min), and total hemodynamic events (including any abnormal blood pressure events and arrhythmias) were recorded. Postoperative complications in the PACU were documented including dizziness, nausea, vomiting, shivering, hoarseness in voice, agitation, delirium, and any other complaint from the patient. The endoscopist assessed the ease of performing ERCP immediately after the operation (1 = poor, 2 = fair, 3 = good, 4 = excellent,). Patient satisfaction was assessed before they left the PACU (1 = unbearable, 2 = very uncomfortable, 3 = slightly uncomfortable, and 4 = no discomfort). All adverse events during this study were monitored and followed by the investigator until conversion to normal or no clinical treatment being necessary. Serious

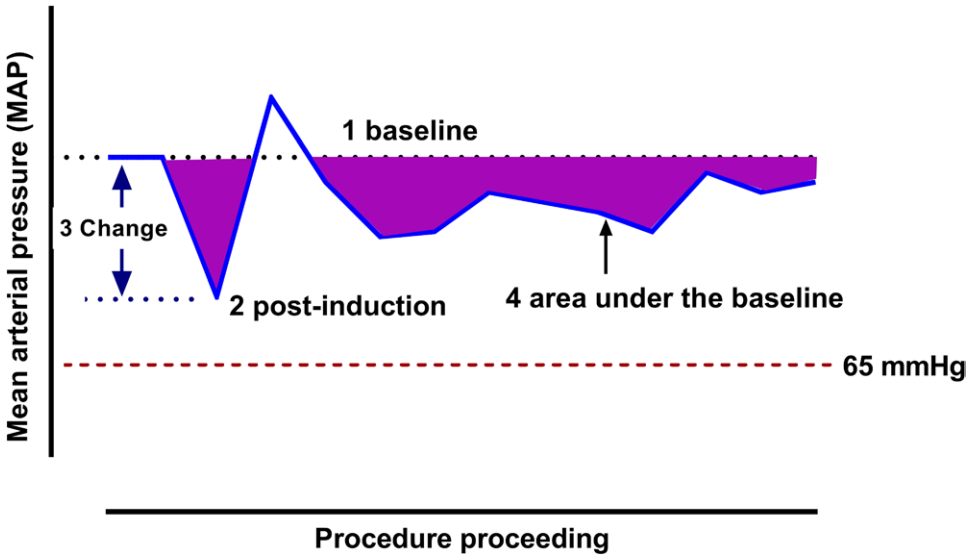

Figure 1. Schematic illustration of blood pressure parameters. (1) Baseline MAP on admission to endoscopy room. (2) MAP after induction success. (3) Changed value compared to the baseline MAP. (4) The AUB was measured by calculating the difference of the MAP (compared to baseline) × time in minute when below the baseline. AUB indicates the area under baseline; MAP, mean arterial pressure

adverse events for this research included postoperative mortality, ICU admission, reported organ dysfunctions such as cardiac dysfunction, acute kidney injury, postoperative hemorrhage, and unexpected reoperations, leading to extended hospital stays.

Statistical Analysis

Data were analyzed in the modified intention-to-treat (ITT) population, which included all the randomized patients who received at least 1 dose of trial medication. To assess the baseline balance between groups, we calculated the absolute standardized difference (ASD) for baseline characteristics, including demographics, indications for procedure, preoperative vital signs, anesthetic infusion rates, intravenous fluid totals, and the duration of the procedure and anesthesia. Differences greater than $1.96 \times \sqrt{\frac{1}{N1} + \frac{1}{N2}}$ (N1, Number of participants in group 1; N2, Number of participants in group 2) were considered imbalanced.[24] Calculated differences >0.438 were considered imbalanced in this trial.

Continuous variables are presented as median [Q1–Q3] or mean with standard deviation (SD) when normally distributed. Normally distributed variables were analyzed using Student *t* test, while nonnormally distributed variables were analyzed using the Mann-Whitney *U* test. Differences in means or median differences, along with 95% confidence intervals (CIs), are provided where appropriate. The change in MAP during induction, AUB throughout the procedure, time-weighted average of AUB, cumulative time of hypotension, total amount of metaraminol, change in MAP after airway placement, change in HR after induction, and change in HR after airway placement were analyzed using the Mann-Whitney *U* test and the Hodges-Lehman median difference with a 95% CI. The lowest MAP was analyzed with Student *t* test. Categorical variables are presented as numbers and percentages and analyzed using χ^2 or Fisher's exact tests or continuity correction when appropriate.

To assess the treatment effect heterogeneity between levels of specified baseline variables, subgroup analyses were performed including age (<60 or ≥60 years), sex (male or female), and bilirubin concentrations (total bilirubin ≥17.1 μmol/L or <17.1 μmol/L). Generalized linear models were used to estimate the interaction effects between the primary outcomes (ie, changes in MAP by induction and AUB through the procedure) and subgroup variables. To account for multiple comparisons, a Bonferroni correction for the significance criterion for each interaction was set to.05/3 =.017.

A 2-sided *P*-value of.05 was considered statistically significant. The significance levels for the primary outcomes were.025 (ie, 05/2, Bonferroni correction). Because of the potential type I error due to multiple comparisons, findings from analysis of secondary outcomes should be interpreted as exploratory. The significance levels were.0063(0.05/8) adjusted by Bonferroni correction for secondary outcomes. All analyses were conducted with IBM SPSS Statistics ver. 25.0 (SPSS Inc), and figures were constructed using GraphPad Prism ver. 8.0.

Sample Size

The sample size was determined based on 2 primary outcomes, with a significance level (α) of 0.05 equally distributed, assigning 0.025 to each outcome. The change in MAP from baseline to successful induction with propofol, reported as mean (SD), was 26.7 mm Hg (SD = 9.1 mm Hg) according to a previous study.[25] Assuming that a reduction in MAP by 20% or more constituted a clinically meaningful effect,[26] given an MAP range of 70 to 105 mm Hg, the change in MAP

ranged from 14 to 21 mm Hg, with a midpoint of 17.5 mm Hg. Thus, the assumed difference of changed MAP between groups was calculated as 9.2 mm Hg (26.7–17.5 = 9.2 mm Hg). Using power and sample size software (PASS ver. 11.0), we set the assumed mean difference at 9.2 mm Hg, with an SD of 9.1 mm Hg (assuming equal variance), with a significance level of 0.025 and 90% power, and accounting for a 20% dropout rate, a sample size of 40 patients per group was estimated. Limited data are currently available for the other primary outcome, AUB. According to our pilot study, AUB was 650 mm Hg·min (SD = 350 mm Hg·min) in the propofol group and 311 mm Hg·min (SD = 262 mm Hg·min) in the remimazolam group. A reduction of 50% in the area under blood pressure threshold was considered clinically meaningful based on prior literature.[23] Assuming a mean difference of 325 mm Hg·min on AUB, and using a significance level of 0.025 with 90% power, given a 20% dropout rate, each group would require 38 patients. Consequently, the final sample size was estimated to be 80 patients, with 40 in each group.

RESULTS

Characteristics of the Patients

Ninety-one patients scheduled for therapeutic ERCP were screened for eligibility. Eleven patients were excluded for the following reasons: 2 patients for suspected difficult airway, 3 for uncontrolled hypertension, and 6 who declined to participate in the trial. A total of 80 patients were enrolled and randomly allocated to either the remimazolam and propofol groups (Figure 2). No patient dropped out after randomization and all randomized patients were analyzed. Similar baseline characteristics were observed in the randomized patients and all ASDs were <0.438 (Table 1). Anesthesia was successfully induced in all patients.

Primary Outcomes

The change in MAP from baseline to induction success and the AUB are presented in Figure 3. The change in MAP from baseline to induction success was significantly smaller in the remimazolam group than that in the propofol group. The AUB was significantly lower in the remimazolam group compared to the propofol group.

Secondary Outcomes

Table 2 presents the secondary outcomes. When corrected with the anesthesia time, the time-weighted average of AUB was significantly lower in the remimazolam group than in the propofol group. Throughout the procedure, 2 and 12 patients experienced 1 or more hypotensive episodes in the

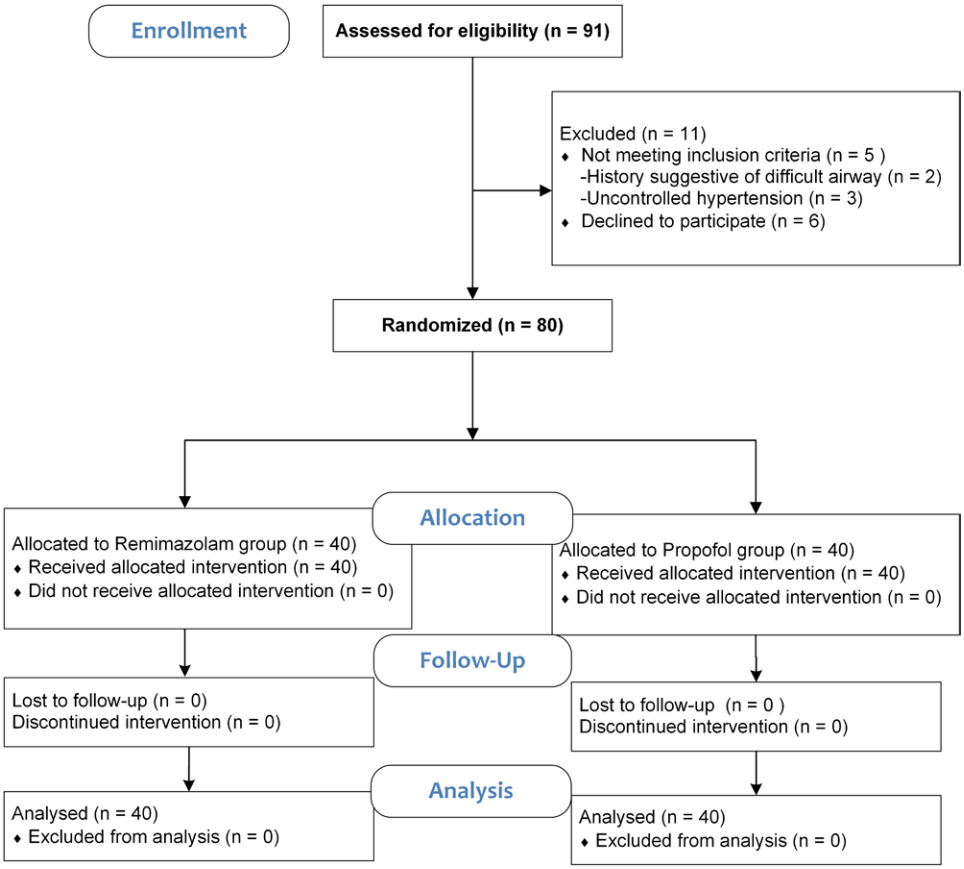

Figure 2. CONSORT flow chart of the trial. CONSORT indicates Consolidated Standards of Reporting Trials.

Table 1. Patient Demographics and Clinical Characteristics

	Remimazolam (n = 40)	Propofol (n = 40)	Absolute standardized difference
Age, y	54 [45–63]	59 [51–67]	.282
Sex, male, n (%)	22 (55)	24 (60)	.101
Body mass index, kg·m^{-2}	20.4 [19.4–23.0]	21.6 [19.5–23.3]	.249
ASA classification, n (%)			
I	1 (2.5)	0 (0)	.226
II	30 (75)	31 (77.5)	.059
III	9 (22.5)	9 (22.5)	.000
Indications, n (%)			
Biliary calculi	15 (37.5)	13 (32.5)	.105
Biliary tract tumor	14 (35)	17 (42.5)	.154
Pancreatic disease	10 (25)	9 (22.5)	.059
Posttransplantation	1 (2.5)	1 (2.5)	.000
Preoperative status			
Hemoglobin, g/L	120 ± 21	123 ± 21	.132
Total protein, g/L	67 ± 7	68 ± 9	.231
Albumin, g/L	38 ± 6	39 ± 7	.101
Alanine transaminase, U/L	42 [20–114]	52 [22–81]	.317
Aspartate transaminase, U/L	51 [20–154]	45 [22–74]	.314
Total bilirubin, μmol/L	25 [12–90]	23 [11–120]	.008
Creatinine, μmol/L	64 [53–75]	71 [60–83]	.255
Length of hospital stay, d	7 [1–11]	7 [1–15]	.052

Continuous variables are expressed as median [Q1–Q3] or the mean ± standard deviation, and categorical variables as numbers (%).
Absolute standardized difference is the absolute difference in group means divided by the pooled standard deviation. Calculated differences >0.438 were considered imbalanced in this study.
Abbreviations: ASA, American Society of Anesthesiologists; bpm, beat per min; HR, heart rate; MAP, mean arterial pressure.

remimazolam and propofol groups, respectively. The remimazolam group experienced a shorter duration of hypotension than the propofol group. The change in MAP after airway placement, the change in HR after induction, and change in HR after airway placement were lower in the remimazolam group.

The preoperative baseline vital signs, the duration of procedure, the duration of anesthesia, the average remifentanil infusion rate, and the total amount intravenous fluid administered were similar between groups. Abnormal hemodynamic events, the total number of postoperative complications, and satisfaction scores from patients and endoscopists for the remimazolam and propofol groups are presented in Table 3. Outcomes during the recovery phase were also reported descriptively, as our hospital routinely use flumazenil to reverse remimazolam, potentially confounding the true effect of remimazolam. No adverse events occurred throughout the procedure that necessitated the replacement of the supraglottic airway with an endotracheal tube. No serious adverse events occurred in either group.

Assessment of Treatment Effect Heterogeneity

Post hoc analysis demonstrated that age (≥60 or <60 years), sex (male or female), or bilirubin level (total bilirubin ≥17.1 μmol/L or <17.1 μmol/L) were not effect modifiers for the relationship between remimazolam and the change in MAP after induction (all *P*-values for interaction >0.017, as shown in Supplemental Digital Content 2, Supplementary Figure S2, http://links.lww.com/AA/F102). Similarly, age, sex, or the bilirubin concentration also did not act as effect modifiers for the relationship between remimazolam and the AUB throughout the procedure (none were significant, as illustrated in Supplemental Digital Content 2, Supplementary Figure S2, http://links.lww.com/AA/F102).

DISCUSSION

The present randomized controlled trial showed that in GA for therapeutic ERCP, remimazolam produced less of drop in MAP during induction and maintenance of anesthesia, in comparison to propofol.

Our findings are consistent with prior work. In a study comparing MAP changes during induction with remimazolam or propofol in patients undergoing mitral and/or aortic value replacement, Liu et al[25] reported less of a blood pressure drop with remimazolam 19 ± 7 mm Hg than with propofol 27 ± 9 mm Hg (mean ± standard deviation). The drop in blood pressure with remimazolam was more pronounced than what we observed (−7.5 [−14.0 to 0] mm Hg) perhaps due to the use of a larger remimazolam dose (0.3 mg/kg vs 0.2 mg/kg used in our study).

In another study, researchers compared the percentage of patients that developed hypotension during an ERCP between remimazolam-alfentanil and propofol-alfentanil.[27] In a similar fashion to our study the authors defined hypotension as MAP <65 mm Hg but also added a decrease of > 20% from baseline, without mentioning duration. They found that the percentage of patients that

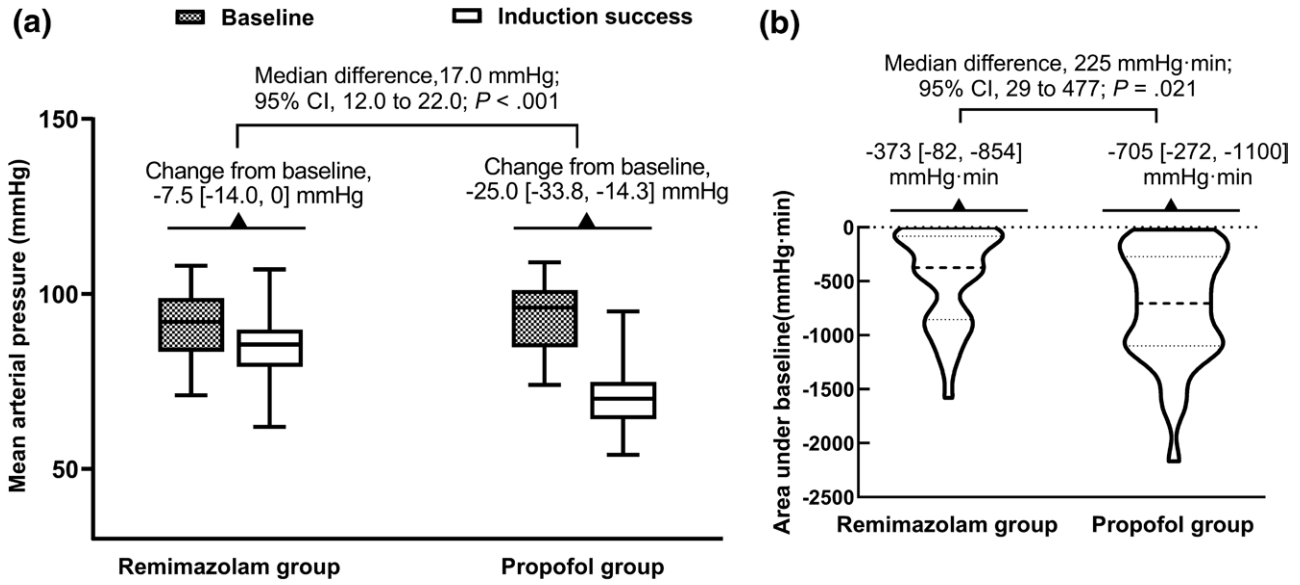

Figure 3. Comparison of the change in MAP (a) and the AUB (b) between the remimazolam and propofol groups. *P* values <.025 indicates statistical significance (Bonferroni correction). A, The change in MAP was calculated as the difference between baseline MAP (plaid box) and MAP at successful induction (white box), with median values shown by the lines within the boxes and interquartile range indicated by box width. The induction success required both loss of response to a shoulder shake and BIS <60. The change in MAP in the remimazolam group was lower than in the propofol group, with a median difference of 17.0 mm Hg using Mann-Whitney *U* test and Hodges–Lehman estimate (*P* < .001). B, Violin plots show medians (thick dashed Line) and the 25th and 75th percentiles (thin dotted line). The AUB for remimazolam was smaller than that for propofol, with a median difference of 255 mm Hg·min (*P* =.021). AUB indicates the area under baseline; BIS, bispectral index; CI, confidence intervals; MAP, mean arterial pressure.

developed hypotension were 17.6% and 35.2%, for remimazolam-alfentanil and propofol-alfentanil, respectively. By comparison, we found the percentage of patients with a drop in blood pressure defined as an MAP <65 mm Hg for >1 minute to be 5% and 30% for remimazolam-remifentanil and propofol-remifentanil, respectively.

Several prior studies using a variety of thresholds in the magnitude and duration of low blood pressure have connected low blood pressure with the risk of acute kidney injury, myocardial injury, postoperative dementia, and 30-day mortality.[10–13] To help put our results into clinical context, it is useful to consider a systematic review of 42 studies exploring the risk of end-organ injury after noncardiac surgery from intraoperative hypotension.[28] They evaluated available data to compile a risk profile based on the magnitude and duration of hypotension. They suggested that a risk of overall organ injury, although low, begins at MAP <80 mm Hg for longer than 10 minutes. They also identified high-risk thresholds as MAP <65 mm Hg for 20 minutes, MAP <50 mm Hg for 5 minutes, or any exposure to MAP <40 mm Hg.

This risk profile provides an interesting framework for interpreting our results. Although patients in our study did not achieve thresholds for high risk of organ injury, patients in the propofol group more than the remimazolam group did achieve thresholds for being at some risk of organ injury. Further investigation is warranted

Table 2. Secondary Outcomes

	Remimazolam (n = 40)	Propofol (n = 40)	Difference (95% CI) or RR (95% CI)	*P* value[a]
Time-weighted average of AUB, mm Hg	−5.5 [−11.2 to −1.3]	−12.9 [−18.6 to −4.8]	4.44 (1.09–7.80)	.010
Hypotension, n (%)	2 (5%)	12 (30%)	0.167 (0.040–0.697)	.006
Total metaraminol, mg	0.0 [0.0–0.0]	0.0 [0.0–0.2]	0.000 (0.000–0.002)	.003
Duration of hypotension, min	0.0 [0.0–0.0]	0.0 [0.0–3.0]	0.000 (0.000–0.001)	.003
Lowest MAP, mm Hg	76 ± 6	69 ± 8	8 (4–11)	<.001
Change in MAP after airway placement, mm Hg	−3.5 [−12.3 to 2.5]	−13.5 [−22.8 to −2.8]	10 (4–16)	.001
Change in HR after induction, bpm	−9 [−12.8 to −5]	−18 [−22 to −14.3]	7 (3–11)	<.001
Change in HR after airway placement, bpm	−1 [−7 to 2]	−3 [−8.8 to 1.8]	1 (−2–5)	.321

Data are expressed as median [Q1–Q3], mean ± SD, or numbers (%). Difference indicated in the mean or median difference (95% CI) depended on the condition. Hodges-Lehmann was used to estimate the median difference between groups. Area under baseline (AUB) of MAP was measured by calculating the difference of the MAP (compared to baseline) × time in minutes when below the baseline. Time-weighted average of AUB was calculated as the AUB divided by anesthesia time.

Abbreviations: AUB, area under baseline; bpm, beat per min; CI, confidence intervals; HR, heart rate; MAP, mean arterial pressure; RR, risk ratio.

[a]*P* < .0063 indicates statistical significance (Bonferroni correction).

Table 3. Perioperative Clinical Characteristics

	Remimazolam (n = 40)	Propofol (n = 40)	Absolute standardized difference
Baseline vital signs			
MAP, mm Hg	91 ± 9	94 ± 10	.223
HR, bpm	77 ± 10	78 ± 8	.136
Pulse oxygen saturation, %	97 [96–98]	97 [95–98]	.176
Anesthetics infusion rate			
Remifentanil infusion rate, μg/kg/min	0.16 [0.15–0.16]	0.16 [0.15–0.17]	.060
Remimazolam infusion rate, mg/kg/h	0.8 [0.8–0.9]	/	
Propofol infusion rate, mg/kg/h	/	4.2 [4.0–4.4]	
Duration of procedure, min	40 [32–64]	35 [30–35]	.391
Duration of anesthesia, min	50 [40–72]	45 [40–73]	.041
Liquid requirement, mL	900 [800–970]	890 [800–988]	.036
Hypertension, n (%)	0 (0)	2 (5)	
Bradycardia, n (%)	3 (7.5)	7 (17.5)	
Tachycardia, n (%)	1 (2.5)	1 (2.5)	
Total hemodynamic events, n (%)	6 (15)	17 (42.5)	
Time to state DOB, min	8.0 [6.0–9.0]	11.0 [10.3–18.0]	
Postoperative complications, n (%)	9 (22.5)	20 (50)	
Satisfaction from patients, n (%)			
Slightly uncomfortable	8 (20)	16 (40)	
No discomfort	32 (80)	24 (60)	
Satisfaction from endoscopists, n (%)			
Poor to fair	1 (2.5)	1 (2.5)	
Good to excellent	39 (97.5)	39 (97.5)	

Continuous variables are expressed as median [Q1–Q3] or the mean ± SD, and categorical variables as numbers (%).

Absolute standardized difference is the absolute difference in group means divided by the pooled SD. Calculated differences >0.438 were considered imbalanced in this study.

Abnormal hemodynamic events in 2 groups and outcomes during the recovery phase were reported descriptively only.Abbreviations: ASA, American Society of Anesthesiologists; bpm, beat per min; DOB, date of birth; HR, heart rate; MAP, mean arterial pressure.

to better understand the harmful implications of these episodes of hypotension in this patient group.

The reduced intervention on blood pressure was beneficial in outpatient ERCPs, enabling anesthesiologists to better manage other aspects. In this trial, all patients were instrumented with an arterial line. This enabled prompt detection and treatment of hypotension if the MAP dropped <65 mm Hg. Consequently, both the remimazolam and propofol groups exhibited short durations of hypotension. We recognize that an arterial line to monitor blood pressure is not commonly utilized for endoscopy procedures. Most patients are likely monitored with intermittent noninvasive blood pressure measurements that do not have the same time resolution as an arterial line. The observed frequency and duration of low blood pressure and use of vasoactive agents may have been different had we conducted this study using a blood pressure cuff instead of an arterial line. We recognize this limits the generalizability of our findings for this type of procedure.

The subgroup analysis was conducted to explore whether jaundice, age, or sex would impair the effect of remimazolam on hemodynamics, as many elderly patients requiring ERCP suffer from obstructive jaundice. They are at a high risk of developing hypotension and bradycardia during anesthesia induction and maintenance, because of decreased sensitivity to both sympathetic and vagal components of the baroreflex.[29] Furthermore, it has been hypothesized that obstructive jaundice may affect the pharmacokinetics and sensitivity of remimazolam.[30] Our subgroup analysis, however, found that the effect of remimazolam on blood pressure did not depend on age, sex, or bilirubin level although the study was underpowered to properly explore these covariates on changes in blood pressure.

The present trial had some limitations. First, the execution of blinding was a challenge because of the formulation appearance of remimazolam versus propofol, the latter being a fat emulsion. As described in the methods section, this was addressed with an additional nonblinded investigator to administer the propofol or remimazolam while keeping those collecting data blinded to which drug was used. Second, an ASA status ≥4 and emergency were excluded from this study for patient safety and ethical concerns, but they might potentially experience heightened benefits from remimazolam. Third, this trial was conducted at 1 center's specific situation, utilizing a laryngeal mask for airway management, with arterial lines for blood pressure monitoring and management, and the regional preference for vasoactive agents such as metaraminol. These circumstances may differ from those of other institutions, thereby to some extent limiting generalizability to other centers. To address this limitation, we look forward to a future randomized controlled trial with a larger sample size in multiple centers. Fourth, Inhalational and intravenous anesthetics are commonly used in

endoscopic procedures. However, this study did not compare inhalational agents such as sevoflurane with remimazolam. Although prior work has established that that intraoperative hypotension is associated with postoperative complications, we did not record any potential adverse events associated with hypotension such as myocardial injury, acute renal injury, or mortality.

In conclusion, this randomized controlled trial showed that remimazolam produced a milder change in MAP during induction and a smaller AUB through the procedure compared to propofol during GA for therapeutic ERCP. Remimazolam may be considered a better choice for complex endoscopic procedures in the outpatient setting, with the potential advantage of stable hemodynamics. ■

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DISCLOSURES

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