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Comparison of Remimazolam and Propofol for Intravenous Anesthesia on Trigeminocardiac Reflex in Percutaneous Balloon Compression for Trigeminal Neuralgia: A Randomized Controlled Trial

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Background: Trigeminal neuralgia usually presents as incapacitating facial pain. Percutaneous balloon compression (PBC) is frequently utilized to manage this ailment. Trigeminocardiac reflex (TCR) commonly presents with sudden severe bradycardia or even asystole, alongside a sudden increase in blood pressure during this surgical procedure. Notably, remimazolam has been reported to maintain higher heart rate (HR) levels during anesthesia than propofol. Thus, this study aims to assess the impact of remimazolam anesthesia versus propofol on TCR occurrence during this procedure.

Methods: This randomized controlled trial involved patients with trigeminal neuralgia scheduled for elective PBC. Patients were randomly assigned to receive either remimazolam or propofol for anesthesia. The primary outcome was the incidence of TCR, a potential complication during the procedure. Secondary outcomes included the occurrence of severe TCR, usage of atropine, HR at the time of foramen ovale puncture (T4), HR at the time of trigeminal ganglion compression (T5), and any adverse events.

Results: A total of 80 patients were included in the study, with 40 patients in each group. The incidence of TCR was significantly lower in the remimazolam group compared to the propofol group (30.0% vs 82.5%; risk difference −52.5%, 95% CI −67.3% to −18.6%; $P < 0.001$). The remimazolam group also showed a lower incidence of severe TCR (7.5% vs 45.0%) and significantly lower usage of atropine compared to the propofol group ($P < 0.001$). Furthermore, HR at T4 and T5 were higher in the remimazolam than in the propofol group ($P < 0.001$). There was no significant difference in the incidence of adverse events between the two groups.

Conclusion: In PBC surgery for trigeminal neuralgia, remimazolam-based intravenous anesthesia showed a higher HR and a lower incidence of TCR than propofol without any increased adverse events.

Keywords: remimazolam, propofol, trigeminal neuralgia, balloon occlusion, methods, reflex, trigeminocardiac, hemodynamics

Introduction

Trigeminal neuralgia is a chronic neuropathic pain condition that causes spontaneous and provoked episodes of electric shock-like or stabbing pain in the facial areas.[1,2] Severe cases of trigeminal neuralgia even have been associated with a diminished quality of life and an increased risk of suicide.[1,3] Percutaneous balloon compression (PBC) of the trigeminal ganglion has become a well-recognized technique for severe trigeminal neuralgia.[4] Significant hemodynamic fluctuations are often observed during the PBC procedure, resulting in a sudden severe bradycardia or even asystole and a sudden increase in blood pressure, known as the trigeminocardiac reflex (TCR).[5,6] Unfortunately, this can lead to disastrous cardiovascular complications and become life-threatening.

Meuwly et al[5] proposed that TCR was defined as a sudden and dramatic change in heart rate (HR), with or without accompanying changes in blood pressure, which indicated that HR fluctuation (bradycardia) is a more important variable

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than changes in blood pressure during the TCR. Prophylactic administration of atropine was suggested to prevent or reduce TCR-related tachycardia,[7] while nitroprusside was used to prevent TCR-related hypertension.[8] Additionally, the combination of nitroprusside and atropine was also employed for TCR pretreatment.[9] Although atropine reduced the incidence of bradycardia, it was associated with potential side effects such as increased blood pressure, arrhythmias, elevated intraocular pressure, and delirium.[6] Moreover, the unpredictability of certain TCR types and the uncertainty regarding the timing of prophylactic administration contribute to the ongoing debate over the atropine-related prevention of TCR.[10] Although various methods to prevent TCR have been explored, such as trigeminal ganglion block,[11] deep anesthesia,[12] using inhalational anesthetics[13] and combined anesthesia,[14] a definitive method for TCR prevention remains elusive.

Although the detailed pathophysiological mechanisms of TCR are unclear, previous studies have indicated that TCR is associated with dysregulation of the parasympathetic and sympathetic nervous systems.[10,15] Remimazolam, a novel anesthetic, has been reported to offer significant advantages in hemodynamic stability in general anesthesia.[16–18] Unlike propofol, which tended to favor sympathetic dominance, remimazolam was reported to maintain the balance between sympathetic and parasympathetic activities.[19] Furthermore, studies have shown that patients receiving intravenous remimazolam anesthesia exhibit higher HRs and a reduced incidence of bradycardia compared to those receiving propofol in different surgeries.[20–22]

Thus, we conducted this study to investigate whether remimazolam, compared to conventional propofol intravenous anesthesia, can reduce the incidence of TCR during the PBC procedure.

Methods

Study Design

The study was a single-center, prospective, double-blinded, parallel-controlled trial conducted at the Second Xiangya Hospital, Central South University, China, from September 2021 to September 2022. This trial was approved by the Clinical Research Ethics Committee of the hospital (No. 2021-062). Additionally, this study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients before enrollment. The study was registered at www.chictr.org.cn (ChiCTR2100049775, principal investigator: YanYing Xiao, registration date: August 09, 2021) prior to patient enrollment.

Participants

Adult patients (≥18 years old) with an American Society of Anesthesiologists (ASA) physical status I–III scheduled for elective percutaneous balloon compression (PBC) of the trigeminal ganglion were included. Exclusion criteria included uncontrolled hypertension (> 160/100 mmHg), bradycardia with HR < 50 beats per minute (bpm), 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 the remimazolam or propofol group at a 1:1 allocation ratio by a computer-generated randomization sequence (simple randomization) using Statistical Product and Service Solutions (SPSS, ver. 25.0, IBM Corp, Chicago, US) software. Due to the distinct appearances of the investigational drugs, a double-blind, double-dummy method was employed to ensure blinding. The group allocations were enclosed in sealed opaque envelopes and provided to non-blinded investigators for drug preparation, while blinded investigators conducted all assessments, data collection, and analysis. Remimazolam appeared as a transparent injectable solution following preparation, with its placebo being a saline injectable solution. In contrast, propofol appeared as a white emulsion, with its placebo being a 10% fat emulsion. For instance, during the induction phase, a 50 kg patient would receive simultaneous intravenous injection of 10 mL of the transparent injectable solution (assuming a concentration of 1 mg/mL for remimazolam) and 10 mL of the white emulsion.

Trial Procedure

All patients received a standard liquid administration following the "4-2-1" protocol. The total liquid requirement (mL) = [40 mL/h + 20 mL/h + (weight - 20) × 1 mL/h] × fasting duration (h), half of which was administrated before induction and half during the following period. Electrocardiogram (ECG), HR, pulse oxygen saturation (SpO_2) and end-tidal carbon dioxide (CO_2) were recorded by the monitor (Dash 5000, General Electric Company, US), and electroencephalography was monitored with bispectral index (BIS) (VT21404, Medtronic, US) throughout the procedure. Continuous arterial blood pressure measurement was achieved through right radial artery catheterization. For induction, patients in the remimazolam group were given 0.2–0.3 mg/kg remimazolam (Yichang Renfu Pharmaceutical Co., Ltd, China), while patients in the propofol group were induced with propofol (AstraZeneca UK Limited) at 2.0–2.5 mg/kg. Subsequently, sufentanil at 0.4 μg/kg and rocuronium at 0.6 mg/kg were administered when the BIS dropped below 60. Moreover, tracheal intubation was conducted upon meeting the intubation criteria. For anesthesia maintenance, the infusion rate of remimazolam (0.5–2.0 mg/kg/h) or propofol (2–8 mg/kg/h) was modified to maintain the BIS value between 40–60 intraoperatively. Meanwhile, the anesthesiologists operated on adjusting the infusion rate of remifentanil (0.1–0.2 μg/kg/min), with an initial infusion rate of 0.1 μg/kg/min.

All procedures using the modified Hartel puncture technique were performed by the same surgeon.[23] The operation to the abnormal hemodynamics was carefully documented, following these rules: if mean arterial pressure (MAP) < 65mmHg or decreased by more than 20% from baseline, intravenous administration of 4μg of norepinephrine was given; if MAP > 120mmHg or increased by more than 20% from baseline, 50μg of nitroglycerin was given; if HR < 50 bpm, 0.25mg of atropine was given and can be repeated; if atropine was ineffective, isoproterenol could be considered. In the event of cardiac arrest during puncture or balloon compression, surgical procedures were immediately halted, and 0.5mg of atropine was administered along with cardiopulmonary resuscitation.

Following completion of the procedure, administration of all medications ceased, and patients were transferred to the Post-Anesthesia Care Unit (PACU). Additionally, the attending anesthesiologist decided on extubation timing and assessed patient recovery in the PACU. Patients were allowed to be transferred to the ward when the modified Aldrete Score achieved 9 points. Furthermore, all adverse events during this study were monitored and followed until conversion to normal or no clinical treatment was necessary.

Outcome Measures

The primary outcome was the incidence of TCR during the procedure. TCR was defined by an absolute HR reduction below 60 bpm, a decrease in HR by 20% or more from the baseline, and/or asystole. Additionally, it was necessary for the TCR to occur during the operation and meet at least one of the principal TCR criteria (reversibility and plausibility), as defined by Meuwly et al.[5,12,24]

Secondary outcomes included: (1) The incidence of severe TCR which was defined by HR ≤ 50 bpm or a decrease more than 30% from the baseline; (2) The usage of atropine; (3) The incidence of arrhythmia, defined as any arrhythmia related to balloon compression other than sinus bradycardia, such as atrial premature beats, ventricular premature beats, conduction blocks, atrial fibrillation; (4) HR at T4 (at foramen ovale puncture); (5) TCR occurrence at T4; (6) HR classification at T4, HR was classified as normal HR (≥60 bpm), mild bradycardia (50–60 bpm), moderate bradycardia (40–50 bpm) and severe bradycardia (≤ 40 bpm); (7) TCR occurrence at T5 (at balloon compression); (8) HR classification at T5; (9) Data (HR, MAP and BIS) plots were documented at the following time-points: patient entering the operation room after a sufficient rest (T0), 1 minute after anesthetic induction (T1), 1 minute after tracheal intubation (T2), 1 minute before needle puncture (T3), at foramen ovale puncture (T4), at balloon compression (T5), 1 minute after balloon compression (T6), at the end of procedure (T7); (10) Consumption of anesthetic drugs; (11) Any adverse events throughout the surgery. (12) Arterial blood samples were obtained at time points T0, T3, T6, and T7. The levels of stress response factors (epinephrine and norepinephrine) and inflammatory markers [interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α)] were measured by enzyme-linked immunosorbent assay (ELISA).

Data were collected using a structured, pre-tested checklist, entered into EpiData version 3.1 (EpiData Association, Odense, Denmark), and subsequently exported to SPSS software for analysis.

Statistical Analysis

In patients with trigeminal neuralgia undergoing PBC treatment, the incidence of TCR under propofol anesthesia has been reported as 86.7%,[7] but the incidence under remimazolam anesthesia remains undocumented. Hence, we conducted a preliminary experiment with ethical approval, enrolling 9 patients in both the propofol and remimazolam groups, with the same protocol as the present study. In the remimazolam group, TCR occurred in 4 patients (44.4%), while in the propofol group, 7 patients (77.8%) experienced TCR. The incidence of TCR in the remimazolam group was approximately 0.6 times that of the propofol group. Therefore, assuming the TCR incidence in the remimazolam group was 0.6 times that of propofol (ie, 86.7% × 0.6 = 52.0%), this represented a 40% reduction in the remimazolam group compared to the propofol group. Using power and sample size software (PASS 11.0), with a significance level of 0.05 ($\alpha = 0.05$) and a power of 90% ($\beta = 0.10$), selecting the *Z*- Test (Pooled) option, and accounting for a 10% dropout rate, an estimated 80 participants (40 per group) are required.

Continuous variables were expressed as either mean (standard deviation) or median (interquartile range), contingent upon their distributions. The Shapiro–Wilk test was used to determine the normality of the distribution. Group comparisons were conducted using the Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages and analyzed using 2-tailed χ^2 tests or the Fisher exact test. Mean/median and risk differences were reported with 95% confidence intervals (CIs) when appropriate. The repeated measurement data were analyzed using the generalized estimating equations method. All statistical tests were two-sided, with statistical significance defined as a P-value < 0.05.

We evaluated treatment effect heterogeneity by examining if the treatment effect varied across specified baseline variables such as gender, age, and ASA physical status. As such, logistic regression and assessment of interaction were employed. The significance criteria for each interaction were adjusted for multiple comparisons using the Bonferroni correction, resulting in a criterion of 0.05/3 = 0.0167. All analyses were conducted using SPSS software, and figures were constructed using GraphPad Prism ver. 8.0.

Results

Characteristics of the Patients

Ninety-four patients scheduled for PBC were screened for eligibility. Fourteen patients were excluded for the following reasons: 2 patients for a history of potentially difficult airway, 4 for uncontrolled hypertension, 2 for bradycardia with HR < 50 bpm, and 6 who declined to participate in the trial. Finally, 80 patients were allocated to the remimazolam or the propofol group (40 in each) (Figure 1). No patient dropped out after randomization, and all randomized patients were analyzed. Similar baseline characteristics were observed in the randomized patients (Table 1).

Primary Outcome

Total TCR incidence was 30.0% (12/40 patients) in the remimazolam group and 82.5% (33/40 patients) in the propofol group, yielding a risk difference of −52.5% (95% CI, −67.3% to −18.6%; $P < 0.001$) (Table 2).

Secondary Outcomes

The incidence of severe TCR was 7.5% (3/40) in the remimazolam group, compared to 45.0% (18/40) in the propofol group. Moreover, the remimazolam group had a significantly lower usage of atropine than the propofol group ($P < 0.001$). The incidence of arrhythmia (excluding bradycardia) did not differ significantly between the two groups ($P = 0.330$).

Prior to the beginning of puncture (T3), the remimazolam group already exhibited a significantly higher HR compared to the propofol group (74.8 ± 7.9 bpm vs 68.2 ± 7.1 bpm; $P < 0.001$). HR at T4 was also higher in the remimazolam group than propofol (65.7 ± 8.3 bpm vs 53.6 ± 7.2 bpm, with a mean difference of 12.1 bpm; 95% CI, 8.7 to 15.6; $P < 0.001$). At T4, the incidence of TCR was significantly lower in the remimazolam group than in the propofol group (27.5% vs 75.0%, $P < 0.001$). Additionally, severe TCR at T4 was lower in the remimazolam group than in the propofol group (2.5% vs 32.5%, $P < 0.001$). At T5, the remimazolam group had significantly lower TCR incidence than the propofol group (27.5% vs 67.5%, $P < 0.001$), but severe TCR occurrence was not significant (5.0% vs 17.5%, $P = 0.077$). Furthermore, the remimazolam group had consistently lower moderate to severe bradycardia at T4 and T5. (Table 2). The perioperative vital sign changes, including MAP, HR and BIS monitoring, in both groups are presented in Figure 2.

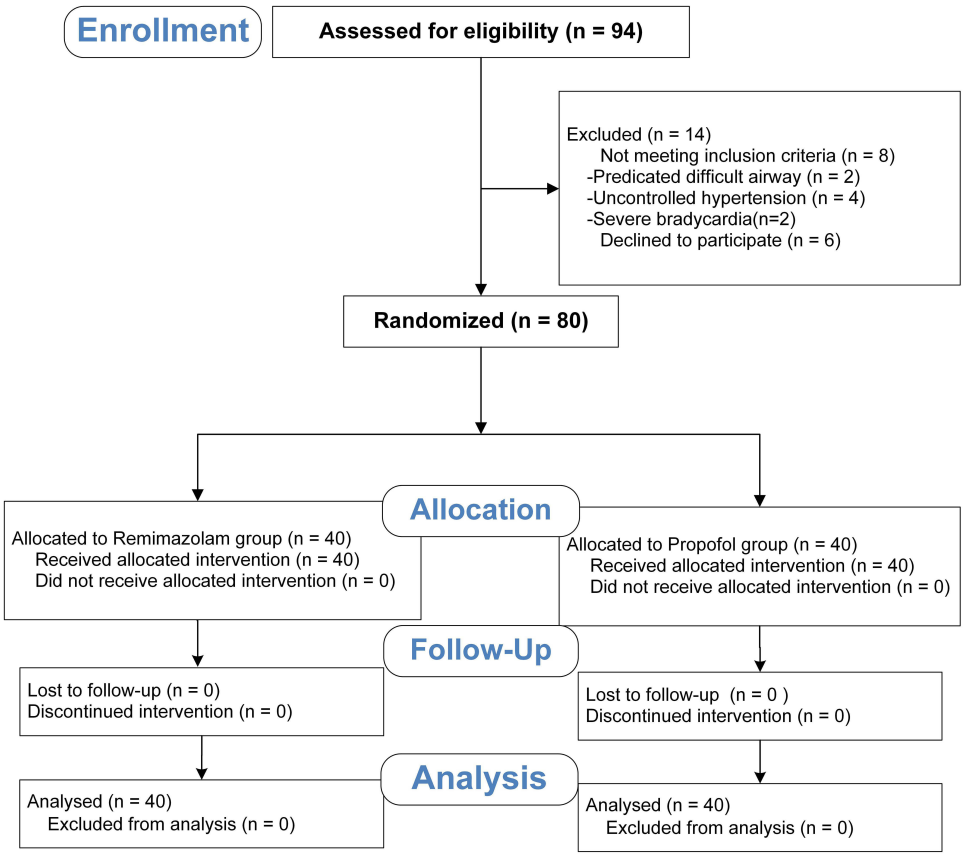

Figure 1 Consort flow diagram of the trial design.

Intra- and Postoperative Characteristics and Adverse Events

No differences in MAP were noted between remimazolam and propofol groups during foramen ovale puncture (T4) and balloon compression (T5), and the nitroglycerin usage was also similar ($P > 0.05$). Intraoperative variables, including balloon compression volume, duration of operation, duration of anesthesia, sufentanil dosage, and remifentanil infusion rate demonstrated no significant differences between the two groups ($P > 0.05$). Postoperative variables, including

Table 1 Patient Demographics and Clinical Characteristics

	Remimazolam Group (n = 40)	**Propofol Group (n = 40)**	**P value**
Age, yr	67 ± 10	69 ± 11	0.434
Sex, Female, n (%)	32 (80)	28 (70)	0.302
ASA physical status, n (%)			0.370
I–II	17 (42.5)	21 (52.5)	
III–IV	23 (57.5)	19 (47.5)	
BMI, kg/m^2	23.2 ± 3.0	24.0 ± 2.8	0.204
Duration of disease, yr	2.0 [1.0–5.8]	3.5 [2.0–6.8]	0.151
Laterality, Left/Right Side, n (%)	20/20 (50.0/50.0)	17/23 (42.5/57.5)	0.501

(*Continued*)

Table 1 (Continued).

	Remimazolam Group (n = 40)	Propofol Group (n = 40)	P value
Involved trigeminal branches, n (%)			0.369
1	26 (65.0)	19 (47.5)	
2	13 (32.5)	19 (47.5)	
3	1 (2.5)	2 (5.0)	
History of hypertension, n (%)	7 (17.5)	8 (20.0)	0.775
History of diabetes, n (%)	7 (17.5)	10 (25.0)	0.412
History of CAD, n (%)	2 (5.0)	1 (2.5)	1.000
Preoperative VAS score	7 [6–8]	7 [6–7]	0.838
Fasting time, hour	8.4 ± 0.8	8.4 ± 1.0	1.000
Preoperative β-blockade, n (%)	2 (5.0)	2 (5.0)	1.000
Liquid administration, mL	830 ± 123	810 ± 109	0.432

Notes: Continuous variables are expressed as medians [IQR] or mean ± standard deviation, and categorical variables as numbers (%).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; CAD, coronary artery disease; VAS, visual analogue scale.

Table 2 Primary Outcome and Secondary Outcomes

	Remimazolam (n = 40)	Propofol (n = 40)	Mean/Median/Risk Difference (95% CI)	*P* value
Total TCR, n (%)	12 (30.0%)	33 (82.5%)	−52.5% (−67.3%, −31.4%)	<0.001
Severe TCR, n (%)[a]	3 (7.5%)	18 (45.0%)	−37.5% (−53.5%, −18.6%)	<0.001
Atropine usage, mg	0 [0–0]	0 [0–0.25]	0 (−0.25, 0)	<0.001
Arrhythmia, n (%)	4 (10.0%)	7 (17.5%)	− 7.5% (−23.2%, 8.2%)	0.330
HR at T3, bpm	74.8 ± 7.90	68.2 ± 7.1	6.6 (3.2, 9.9)	<0.001
HR at T4, bpm	65.7 ± 8.3	53.6 ± 7.2	12.1 (8.7, 15.6)	<0.001
HR at T5, bpm	62.6 ± 7.6	55.7 ± 7.5	7.0 (3.7, 10.4)	<0.001
Change in HR at T4, bpm	9.1 ± 9.2	14.7 ± 7.4	−5.6 (−9.3, −1.9)	0.004
TCR at T4, n (%)	11 (27.5%)	30 (75.0%)	−47.5% (−63.2%, −25.9%)	<0.001
Severe TCR at T4, n (%)	1 (2.5%)	13 (32.5%)	−30% (−45.6%, 13.8%)	<0.001
HR classification at T4, n (%)				<0.001
Normal HR (≥ 60 bpm)	31 (77.5%)	11 (27.5%)	50.0% (28.6%, 65.3%)	
Mild bradycardia (50–60 bpm)	8 (20%)	16 (40%)	−20% (−38%, 0.1%)	
Moderate bradycardia (40–50 bpm)	1 (2.5%)	12 (30.0%)	−27.5% (−43.1%, −11.7%)	
Severe bradycardia (≤ 40 bpm)	0	1 (2.5%)	−2.5% (−12.9%, 6.5%)	

(*Continued*)

Table 2 (Continued).

	Remimazolam (n = 40)	Propofol (n = 40)	Mean/Median/Risk Difference (95% CI)	*P* value
TCR at T5, n (%)	11 (27.5%)	27 (67.5%)	−40% (−56.8%, −18.2%)	<0.001
Severe TCR at T5, n (%)	2 (5%)	7 (17.5%)	−12.5% (−27.4%, 1.9%)	0.077
HR classification at T5, n (%)				0.001
Normal HR (≥ 60 bpm)	30 (75%)	13 (32.5%)	42.5% (20.8%, 58.9%)	
Mild bradycardia (50–60 bpm)	8 (20%)	20 (50%)	−30% (−47.6%, −9.1%)	
Moderate bradycardia (40–50 bpm)	2 (5.0%)	7 (17.5%)	−12.5% (−27.4%, 1.9%)	
Severe bradycardia (≤ 40 bpm)	0	0	0 (−8.8%, 8.8%)	

Notes: Data are expressed as medians [IQR] or mean ± standard deviation, and categorical variables as numbers (%). [a]Severe TCR is defined as HR < 50 bpm or a decrease in HR of 30% or more from the baseline. T3, 1 minute before needle puncture; T4, the moment of foramen ovale puncture; T5, the moment of ganglion compression.
Abbreviations: TCR, trigeminocardiac reflex; HR, heart rate; CI, confidence intervals.

recovery time, time to discharge from the PACU, visual analogue scale (VAS) scores, and incidence of adverse events, did not exhibit statistically significant differences ($P > 0.05$). Furthermore, no serious adverse events occurred in any group (Table 3).

Stress Response Hormones and Inflammatory Factors

Both remimazolam and propofol groups showed similar trends on stress hormones: compared to baseline, stress hormones (epinephrine and norepinephrine) were significantly decreased post-anesthesia, then levels increased dramatically at the end of balloon compression; However, they mostly returned to baseline at the end of surgery ($P < 0.05$). The norepinephrine concentration in the remimazolam group at T3 was significantly lower than that in the propofol group ($P = 0.002$). In contrast, the two groups did not differ in epinephrine levels ($P > 0.05$). Furthermore, the inflammatory factors (IL-6 and TNF-α) concentration did not change significantly over time in either group and was not different between the two study groups ($P > 0.05$) (Table 4).

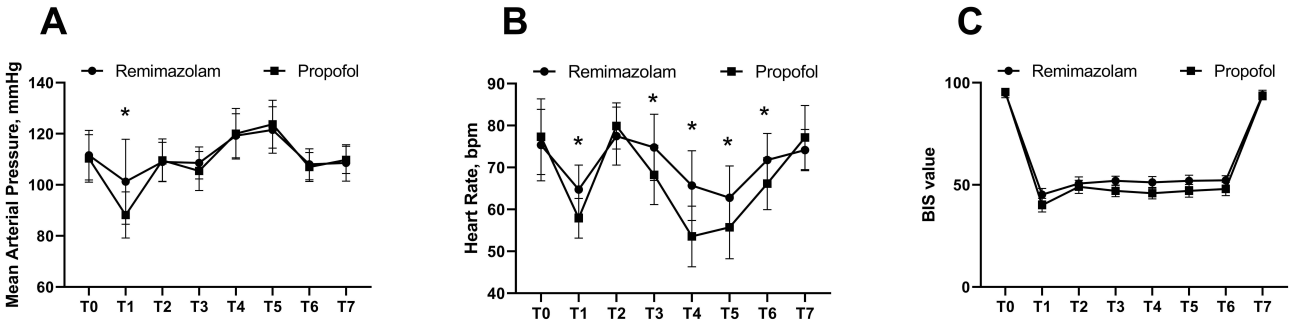

Figure 2 Comparison of MAP, HR, and BIS value between remimazolam and propofol groups at different moments. (**A**) Comparison of MAP between the two groups (*Compared to T0, $P < 0.05$); (**B**) Comparison of HR between the two groups (*Compared to T0, $P < 0.05$); (**C**) Comparison of BIS value between the two groups. T0, 5 minute after the patient entered the operating room; T1, 1 minute after anesthesia induction; T2, 1 minute after tracheal intubation; T3, 1 minute before needle puncture; T4, at foramen ovale puncture; T5, at ganglion compression; T6, 1 minute after ganglion compression; T7, at the end of the procedure.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; BIS, bispectral index.

Table 3 Intra- and Postoperative Characteristics

	Remimazolam (n = 40)	Propofol (n = 40)	Mean/Median/Risk Difference (95% CI)	*P* value
HR at baseline, bpm	75.4 ± 8.5	77.3 ± 9.0	−2.0 (−5.9, 1.9)	0.317
MAP at baseline, mmHg	111.6 ± 9.7	110.3 ± 9.3	1.3 (−3.0, 5.5)	0.558
MAP at T4, mmHg	119.2 ± 8.6	120.0 ± 10.0	−1 (−5.0, 3.3)	0.701
MAP at T5, mmHg	121.5 ± 9.0	123.7 ± 9.3	−2.3 (−6.4, 1.9)	0.279
Nitroglycerin usage, μg	50 [50–50]	50 [50–50]	0 (0, 0)	0.366
Ballon volume, mL	0.50 [0.40–0.55]	0.50 [0.40–0.60]	−0.05 (−0.1, 0)	0.224
Duration of Impression, min	2.5 [2.0–3.0]	2.5 [2.1–3.0]	0 (0, 0)	0.753
Duration of operation, min	40 [30–45]	40 [30–55]	0 (−10, 5)	0.635
Duration of anesthesia, min	55 [49–65]	60 [46–70]	−5 (−15, 0)	0.15
Remifentanil dosage, mg	0.46 [0.40–0.59]	0.47 [0.37–0.60]	0 (−0.04, 0.08)	0.731
Remifentanil infusion rate, μg/kg/min	0.10 ± 0.01	0.10 ± 0.01	0 (−0.003, 0.003)	0.622
Sufentanil dosage, ug	30 [25–34]	30 [25–30]	0 (0, 5)	0.884
Time for eyes opening, min	14.5 [11.3–24]	18 [13–25]	−2 (−5, 0)	0.11
Time for extubation, min	20 [17–27]	23.5 [18–30]	−2 (−6, 1)	0.151
Time for discharge, min	36.5 [32.3–43.0]	40 [35.0–46.5]	−3 (−1, 0)	0.073
Postoperative VAS score	3.0 [2.0–3.0]	2.5 [2.0–3.0]	0 (0, 1)	0.209
Postoperative complications, n (%)	7 (17.5%)	14 (35.0%)	−17.5% (−35.3%, 1.9%)	0.075
Length of hospital, day	2.7 [2.1–3.7]	3.1 [2.5–3.9]	−0.346 (−0.779, 0.096)	0.102

Notes: Data are expressed as mean ± standard deviation, n (%), or median (interquartile range). T4, the moment of foramen ovale puncture; T5, the moment of ganglion compression.
Abbreviations: HR, heart rate; MAP, mean arterial pressure; CI, confidence intervals; VAS, visual analogue scale.

Table 4 Stress Response Hormones and Inflammatory Factors

Variables	T0	T3	T6	T7	Wald	*P* value
Epinephrine, pg/mL						
Remimazolam (n = 40)	47.60 ± 17.00	31.59 ± 13.35	83.45 ± 23.23	52.73 ± 19.00	502.844	<0.001
Propofol (n = 40)	46.58 ± 16.23	29.85 ± 13.54	79.36 ± 21.18	53.98 ± 15.92	297.780	<0.001
t	0.28	0.58	0.82	−0.32		
P	0.784	0.564	0.413	0.751		
Norepinephrine, pg/mL						
Remimazolam (n = 40)	191.69 ± 34.87	130.00 ± 20.99	313.93 ± 64.73	197.24 ± 27.24	432.289	<0.001
Propofol (n = 40)	190.36 ± 30.27	127.06 ± 18.88	362.90 ± 74.48	201.09 ± 29.45	4259.422	<0.001
t	0.18	0.66	−3.14	−0.61		
P	0.856	0.512	0.002	0.546		

(*Continued*)

Table 4 (Continued).

Variables	T0	T3	T6	T7	Wald	*P* value
IL-6, pg/mL						
Remimazolam (n = 40)	9.33 ± 3.01	9.18 ± 4.14	9.25 ± 4.45	9.31 ± 3.47	0.047	0.997
Propofol (n = 40)	9.37 ± 4.04	9.26 ± 3.33	9.39 ± 4.08	9.47 ± 2.74	0.138	0.987
t	−0.05	−0.09	−0.15	−0.22		
P	0.962	0.93	0.878	0.823		
TNF-α, pg/mL						
Remimazolam (n = 40)	12.62 ± 4.79	12.46 ± 4.43	12.40 ± 3.07	12.28 ± 2.48	0.183	0.98
Propofol (n = 40)	12.95 ± 5.38	12.65 ± 6.22	12.58 ± 5.01	12.66 ± 2.86	0.336	0.953
t	−0.28	−0.16	−0.19	−0.63		
P	0.777	0.872	0.847	0.532		

Notes: Data are expressed as mean ± standard deviation. T0, 5 minute after the patient entering the operating room; T3, 1 minute before needle puncture; T6, 1 minute after ganglion compression; T7, at the end of the procedure.
Abbreviations: IL-6, interleukin; TNF-α, tumor necrosis factor α.

Assessment of Treatment Effect Heterogeneity

Post hoc analysis indicated that neither gender, age, nor ASA physical status served as the effect modifier for the relationship of remimazolam and TCR occurrence (*P* value for interaction = 0.297, 0.632, and 0.560, respectively) (Figure 3).

Discussion

This study showed that compared to propofol, remimazolam-based intravenous anesthesia significantly reduced the incidence of TCR (30.0% vs 82.5%) in PBC surgery for trigeminal neuralgia. Additionally, it decreased the occurrence of severe TCR and the use of atropine. At the moment of foramen ovale puncture and balloon compression, the remimazolam group exhibited a higher HR than the propofol group.

PBC is a common treatment option for trigeminal neuralgia due to its demonstrated efficacy.[1,4,10] However, PBC-induced TCR typically results in abrupt hemodynamic changes, particularly during the puncture of the foramen ovale and compression of the trigeminal ganglion.[5,6] Although the pathophysiological mechanisms underlying TCR remain unclear, recent studies have emphasized the involvement of the trigeminal ganglion as a specific subtype of this reflex, in which

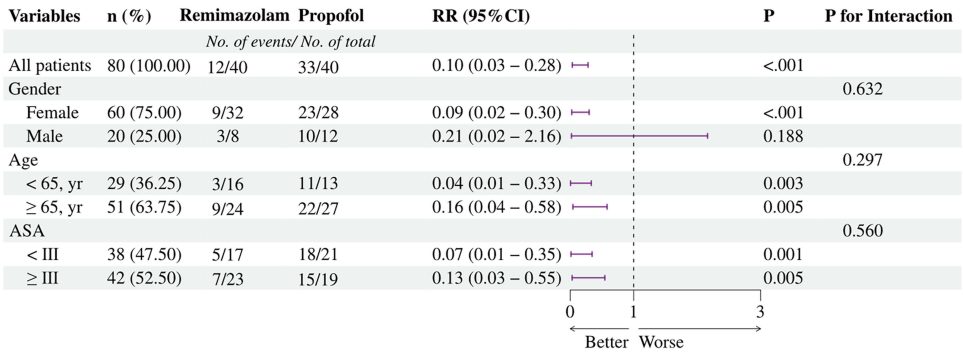

Figure 3 Assessment of treatment effect heterogeneity. *P* values for interaction less than 0.0167 indicate statistical significance after Bonferroni correction. The *P*-values for all interactions are greater than 0.0167, indicating that there is no interaction between the subgroup factors (gender, age, and ASA physical status) and the intervention (remimazolam anesthesia).
Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; RR, relative risk.

both the sympathetic and parasympathetic nervous systems are activated.[6] Moreover, TCR is usually observed in various head-neck surgeries, such as dental, ocular, nasal, faciomaxillary, neurovascular, neurointerventional, and trigeminal rhizolysis procedures.[25–28] It was hypothesized that TCR manifested as bradycardia, asystole, and hypotension in peripheral and central surgeries, whereas in procedures performed on the trigeminal ganglion like PBC, TCR manifested as bradycardia, cardiac arrest, and hypertension.[6]

Remimazolam is a new anesthetic widely used in general anesthesia in recent years. This study demonstrates that in the PBC procedure, compared to the propofol group, HRs during remimazolam anesthesia are higher at multiple time points, including anesthesia maintenance, foramen ovale puncture, and balloon compression. Several studies have reported hemodynamic stability during remimazolam anesthesia, with higher HRs and a lower incidence of bradycardia than propofol in various surgeries.[20–22,29] One study in healthy volunteers showed that the maximum HR increased by 28% after intravenous infusion of remimazolam.[29] However, there was no evidence of any clinically significant impact of remimazolam on cardiac repolarization in procedural sedation and anesthesia.[29,30] Furthermore, one study found that remimazolam and propofol decreased autonomic nervous system activity during anesthesia; however, remimazolam maintained a balance between the sympathetic and parasympathetic systems, which may partially account for heart rate regulation during remimazolam anesthesia.[19]

In previous studies, TCR was defined as a sudden decrease in HR below 60 bpm or by 20% or more from the baseline and/or asystole, with or without a change in blood pressure, during manipulation of the TCR arc pathway.[5] TCR occurs mainly at the time of foramen ovale puncture and is followed by a further decrease in HR and a further increase in blood pressure during subsequent balloon compression. In this study, the overall incidence of TCR in the propofol group (82.5%) was similar to that reported by Wang et al (86.7%).[7] Notably, Wang et al used atropine prophylactically before foramen ovale puncture, reducing TCR incidence to 10%,[7] which was lower than the 30% observed in our remimazolam group. However, the atropine group experienced a significant increase in blood pressure during balloon compression, while remimazolam group in our study showed no significant changes in blood pressure compared to the control group. Another study also reported that pre-treatment with atropine resulted in an increased risk of hypertension, tachycardia, and arrhythmia, complicating hemodynamics.[31] Furthermore, the prophylactic administration of combined atropine and nitroprusside reduced bradycardia during the puncture, but significantly increased tachycardia during subsequent balloon compression, posing challenges for those patients at risk of myocardial ischemia.[9]

Zhang et al[11] included elderly patients aged ≥65 in their PBC procedure study. They defined TCR as an HR below 50 bpm due to the increased vagal characteristics in older adults and reported TCR incidence as 34.2%. In our study, patients aged ≥65 constituted 63.75% of the included participants (average age 68 years, consistent with the demographic of trigeminal neuralgia). Severe TCR was defined as HR below 50 bpm or a change greater than 30%, with a severe TCR incidence of 45% in the control group. The discrepancy may be related to our broader definition of severe TCR, which includes both criteria. Notably, Zhang et al[11] reported no occurrences of HR below 50 bpm in the trigeminal ganglion block group. In contrast, our remimazolam group exhibited a 7.5% incidence of severe TCR, with no occurrences below 40 bpm. However, it is important to note that trigeminal ganglion block has been reported with adverse effects such as pupil dilation,[32] raising concerns about its safety. In comparison, remimazolam, a commonly used sedative for general anesthesia, poses no additional risks.

From an anesthetic perspective, anesthesia has significantly varying effects on the frequency and severity of TCR episodes. The protective impact of total intravenous anesthesia versus volatile anesthesia remains unclear due to inadequate well-designed randomized controlled trials.[13] However, studies have shown a correlation between anesthesia depth and TCR occurrence, suggesting that lighter anesthesia may increase the probability of TCR episodes.[12] Conversely, one study found that increasing the depth of anesthesia with propofol to a BIS level below 40 before puncture did not influence TCR incidence.[33] To minimize the influence of anesthesia depth on TCR outcomes, we utilized total intravenous anesthesia in the two groups, maintained a similar and appropriate anesthesia depth by BIS monitoring, and pumped remifentanil at the same infusion rate. Moreover, various perioperative factors influence intraoperative HRs. In this study, Preoperative medications such as beta-blockers, fasting duration, and fluid administration were balanced and comparable between the two groups. Although the number of patients with hypertension or diabetes was numerically higher in the propofol group, the differences were not statistically significant. It is important to

note that many patients with trigeminal neuralgia have comorbid hypertension and/or diabetes, highlighting the necessity of addressing the interests of this patient population. Future studies with larger sample sizes may provide better insights into the outcomes for this group.

Our findings suggested that patients under anesthesia experienced reduced stress response, with significant decreases in epinephrine and norepinephrine. However, stress hormones significantly increased during balloon compression, particularly norepinephrine, which may be related to the activation of sympathetic nerve fibers in the trigeminal ganglion during balloon compression.[10] Interestingly, the increase in hormones was more pronounced in the propofol group. This is similar to findings in two studies of hip replacement surgery in which remimazolam reduced stress response hormones than propofol.[34,35] Similar to Sun's study,[35] we did not observe changes in IL-6 and TNF-α in the early postoperative period. One article explains this by noting that unlike norepinephrine, which can be produced 15 minutes after stress response, IL-6 may be produced 2 hours after stress stimulation, peak at 4 hours, and persist for a longer duration.[36] Moreover, an animal study reported that remimazolam can reduce the level of endotoxin-induced inflammatory factors (like TNF-α and IL-6) induced by endotoxins and improve the survival rate of endotoxemic mice.[37]

In the current study, remimazolam-based intravenous anesthesia reduced the incidence of TCR. Nonetheless, the efficacy of remimazolam in all patients undergoing anesthesia for PBC remains uncertain. Noteworthy findings from our subgroup analysis reveal that remimazolam's impact on TCR is independent of gender, age, and ASA physical status. However, due to the limited sample size, the heterogeneity tests were still relatively underpowered.

Nevertheless, the present trial had some limitations. First, the blinding process was challenging due to the different appearances of remimazolam and propofol, with the latter being a fat emulsion. To address this concern, a double-blind, double-dummy method was employed to ensure the highest level of blinding. Second, patients with an ASA physical status ≥IV were excluded from the study for safety and ethical reasons. However, these patient populations are crucial for PBC procedures and may benefit significantly from remimazolam. Finally, it is essential to note that this was a single-center study, and caution should be exercised when generalizing the findings. Although the sample size was scientifically determined, it was not particularly large in this trial.

Conclusion

In PBC surgery for trigeminal neuralgia, remimazolam-based intravenous anesthesia showed higher intra-operative HRs and a lower incidence of TCR compared to propofol. Therefore, remimazolam may be a suitable sedative agent for general anesthesia in this procedure.

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Disclosure

The authors disclose no conflicts of interest with respect to this work.

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