Submitted: 08 August, 2023 Accepted: 13 October, 2023 Published: 08 March, 2024 DOI:10.22514/sv.2024.029

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ORIGINAL RESEARCH

Comparison of remimazolam tosylate and propofol in patients undergoing general anesthesia using a laryngeal mask airway without muscle relaxants

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Abstract

It has been reported that anesthesia using propofol can frequently induce hypotension. Herein, we designed this study to compare the incidence of hypotension induced by propofol or remimazolam during laryngeal mask airway (LMA) anesthesia without muscle relaxants. 95 patients aged 18 to 65 years undergoing LMA anesthesia without muscle relaxants were randomly allocated to two groups. After 0.2 µg/kg sufentanil, Group P received a bolus dose of 2 mg/kg propofol followed by a continuous propofol infusion, while Group R received a bolus dose of 0.3 mg/kg remimazolam followed by a continuous remimazolam infusion. The primary outcome was hypotension, defined as systolic blood pressure falling below 90 mmHg during anesthesia. Secondary outcomes included other adverse events. The success rate of initial LMA insertion, LMA insertion conditions, LMA removal time and changes in bispectral index (BIS) and hemodynamics during anesthesia induction, were also assessed. The results showed that the incidence of hypotension was not significantly different between the two groups (47.9% in group P and 36.2% in group R, $p = 0.246$). However, the BIS and heart rate during induction of anesthesia were significantly higher in group R than in group P ($p < 0.05$). Also, hiccups were more common in group R than in group P (14.9% *vs.* 2.1%, $p = 0.031$), and the LMA removal time was significantly longer in group R than in group P (12 min *vs.* 8 min, $p = 0.001$). We did not find a significantly lower incidence of hypotension in patients undergoing LMA anesthesia without muscle relaxants when comparing remimazolam to propofol, potentially related to the study's small sample size, and conducting a large-scale study using similar conditions could be inappropriate due to the risk of remimazolam-induced hiccups.

Keywords

Remimazolam; Propofol; Laryngeal mask airway; Muscle relaxant; Hiccup

1. Introduction

The Laryngeal mask airway (LMA) is a widely used supraglottic airway device in general anesthesia, eliminating the need for vocal cord visualization and reducing airway stimulation, making muscle relaxants unnecessary for LMA anesthesia [1]. This approach minimizes the risk of anaphylaxis and residual effects associated with muscle relaxants, particularly in short-duration surgeries [2].

Propofol is a commonly used intravenous anesthetic with rapid onset and offset, frequently employed for anesthesia induction and tracheal intubation. Propofol can also reduce muscle power during deep anesthesia [3], leading to its use in combination with opioids for LMA insertion during anesthesia induction without muscle relaxants [1]. However, propofol is known to cause issues such as hypotension and injection pain, which can be concerning for anesthesiologists.

Remimazolam, a newer benzodiazepine, offers rapid onset and metabolism. Prior studies have suggested that remimazolam anesthesia is associated with fewer adverse events, including hypotension, bradycardia and injection pain, compared to propofol [4, 5]. Recently, several studies showed that remimazolam could be used with opioids for LMA anesthesia without muscle relaxants [6, 7]. Nevertheless, there is limited evidence comparing remimazolam and propofol for LMA anesthesia without muscle relaxants. Thus, we performed this study to provide a comparative analysis of remimazolam and propofol for LMA anesthesia in short-duration surgeries.

2. Methods

2.1 Study design

This single-center, single-blind, randomized, positive-controlled, parallel study was conducted in China from September 2020 to July 2021. The enrolled patients were randomly assigned to two groups (P and R) at a 1:1 allocation ratio using a random number table.

2.2 Eligibility criteria for participants

The study included adult participants aged 18 to 65 years with an American Society of Anesthesiologists (ASA) physical status of I to II and a body mass index (BMI) between 18 and 29 kg/m^2, who were scheduled for elective surgery with a maximum expected duration of 2 hours under LMA anesthesia without the use of muscle relaxants. Exclusion criteria comprised patients with a difficult airway, a history of asthma or upper respiratory tract infection, known allergies to remimazolam, propofol or opioids, uncontrolled hypertension (*e.g.*, systolic arterial pressure (SAP) $>$160 mmHg), and patients undergoing procedures or having conditions that posed a risk of regurgitation, such as gastroesophageal reflux disease, laparoscopic surgery or the Trendelenburg position. Specific criteria for discontinuation were surgery longer than 2 hours, intraoperative use of inhaled anesthetics or muscle relaxants, postoperative use of flumazenil, or other events that interfered with the surgical procedure.

2.3 Interventions

Patients underwent a preoperative fasting period of at least 8 hours for solids and 2 hours for liquids. Upon arrival in the operating room, they were monitored with an electrocardiogram and underwent noninvasive blood pressure, pulse oximetry (SpO_2) and bispectral index (BIS, Covidien LLC, USA). A peripheral intravenous line was established, and a compound sodium chloride solution was administered at a rate of 4 to 6 mL/min. Preoxygenation was performed using a face mask with an oxygen flow of 5 L/min. Intravenous sufentanil 0.2 µg/kg (01A06051, Yichang Humanwell Pharmaceutical Co, Ltd, Yichang, Hubei, China) was administered over 10 seconds, with patients instructed to breathe before losing consciousness. Prior to LMA insertion (GMA, Tianjin MEDAN Medical Corp., China, Fig. 1), lubrication with lidocaine cream was applied, and LMA size selection was based on patient weight (size 3 for 30 to 50 kg, size 4 for 50 to 90 kg). Three minutes after sufentanil administration, sedatives were manually administered within 30 seconds according to randomization. Group P received propofol 2 mg/kg (2005130, AstraZeneca, Caponago, Italy), while group R received remimazolam tosylate 0.3 mg/kg (200419AK, HengRui Medicine, Lianyungang, Jiangsu, China), diluted to 1 mg/mL with normal saline. All drugs were administered *via* a T-connector, with the infusion tube extending 35 cm from the T-connector to the cannulation site on the patient's hand. If patients exhibited reduced breathing during anesthesia induction, manual ventilation was provided. LMA insertion was initiated when BIS $\leq$60. The LMA was inserted by one of two experienced anesthesiologists without assistance, and the insertion condition was graded by the same anesthesiologist according to the criteria listed in Table 1 [7]. If the BIS was still greater than 60 after 1.5 minutes of the sedative bolus, or if patients resisted insertion of the LMA, propofol 0.5 mg/kg or remimazolam 0.05 mg/kg was added at 1-minute intervals. Considering the relationship between remimazolam sedation and BIS was still unclear [8], the LMA could be inserted after two additional boluses of remimazolam if the patient was unresponsive to verbal contact or jaw thrust. After the successful insertion of the LMA, the patients were mechanically ventilated. Ventilation parameters were set as follows: tidal volume 6 to 8 mL/kg, respiratory rate 10 to 15 breaths/min, fresh gas flow 2 L/min, inspired oxygen fraction 40% to 60%, and positive end-expiratory pressure 5 cmH_2O, maintaining end-tidal carbon dioxide pressure at 35 to 45 mmHg. Anesthesia was maintained with propofol at 4 to 10 mg/kg/h in group P and with remimazolam at 0.5 to 2 mg/kg/h in group R, respectively. The sedative infusion rate was adjusted to maintain BIS between 40 and 60. Mean arterial pressure (MAP) changes were kept within 20% of baseline. Additional intraoperative sufentanil 0.1 to 0.2 µg/kg could be administered if analgesia was inadequate, at the discretion of the anesthesiologist. Dopamine 2 mg was administered if SAP fell below 80 mmHg, and atropine 0.5 mg was given for heart rates (HR) under 45 bpm. Ondansetron 8 mg was intravenously administered before the surgery concluded. The sedative infusion ceased upon completion of the final suture. After regaining consciousness and respiration, the LMA was removed, and patients were transferred to the post-anesthesia care unit (PACU).

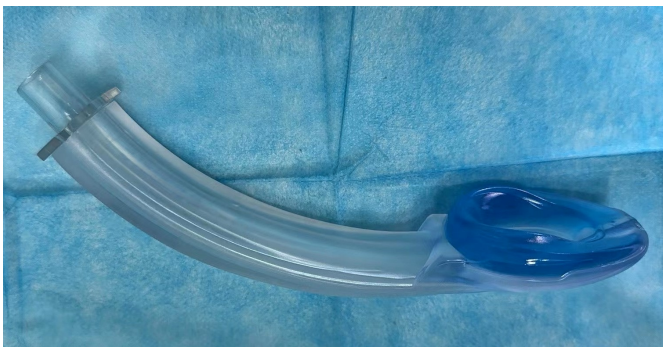

FIGURE 1. GMA laryngeal mask airway.

TABLE 1. The criteria of LMA insertion condition.

Criteria items	Score		
	1	2	3
Mouth opening	Full	Partial	Nil
Swallowing	Nil	Slight	Gross
Coughing	Nil	Slight	Gross
Head or body motion	Nil	Slight	Gross
Laryngospasm	Nil	Mild	Severe
Ease of LMA insertion	Easy	Difficult	Impossible

LMA: Laryngeal mask airway.

2.4 Data collection

Hypotension was defined as an episode of SAP <90 mmHg, while hypertension was defined as SAP ≥180 mmHg, bradycardia as HR <50 bpm, and tachycardia as HR ≥100 bpm, with each event counted as one episode during anesthesia. Injection pain was evaluated by asking patients to respond with "yes" or "no" before, during and after the administration of propofol and remimazolam to assess its incidence. The occurrence of hiccups was defined as hiccups happening after sufentanil administration. Patient HR, SAP, diastolic arterial pressure (DAP), MAP and BIS were recorded at seven time points: immediately before sufentanil administration (T0), 3 minutes after sufentanil administration (T1), immediately before the first LMA insertion attempt (T2), immediately after successful LMA insertion (T3), 2 minutes after LMA insertion (T4), 4 minutes after LMA insertion (T5), and 2 minutes after LMA removal (T6). The LMA insertion score was calculated as the sum of points based on six criteria listed in Table 1, with a total score range of 6 to 18 (a lower score indicating better insertion conditions). Additionally, the study recorded the first attempt success rate for LMA insertion, instances requiring rescue sedation, administration of dopamine, atropine and sufentanil, operative time and LMA removal time. LMA removal time was defined as the duration between the cessation of sedative infusion and LMA removal. Hypoxemia was defined as a single episode of SpO_2 <90%. Shivering was observed after LMA removal and intraoperative awareness was assessed before PACU discharge by simply asking patients if they had any recall during anesthesia.

2.5 Outcomes

The primary outcome was the incidence of hypotension (SAP <90 mmHg) occurring in either group, while secondary outcomes included the incidence of other adverse events (hypertension, bradycardia, tachycardia, injection pain, hiccups, hypoxemia, shivering and intraoperative awareness). Additionally, changes in hemodynamic parameters and BIS values during anesthesia induction, the number of cases requiring rescue sedation for LMA insertion, first attempt LMA insertion success rate, LMA insertion scores, use of dopamine, atropine and intraoperative sufentanil, and LMA removal time were assessed as secondary outcomes.

2.6 Sample size calculation

Sample size calculations were performed using PASS 15.0.5 (NCSS, LLC, Kaysville, Utah, USA). Considering that a previous study reported hypotension incidence rates of 60% for propofol and 34.7% for remimazolam during general anesthesia [4], we assumed that the incidence of hypotension during LMA anesthesia with propofol or remimazolam would be consistent with these prior findings. To achieve 80% statistical power with a one-sided significance level of 0.05, each group required a sample size of 46. In addition, assuming a potential 20% dropout rate, our target enrollment was set at 120 patients.

2.7 Statistical analysis

The data are presented as percentages with corresponding numbers and as means with standard deviations (SD). Statistical analyses were performed using SPSS version 24 (IBM, Armonk, NY, USA). Student *t*-tests were employed to compare patients' age, weight, height, BMI, LMA insertion score, operative time, and LMA removal time. Other demographic data and the incidence of adverse events were compared using either the χ^2 test or Fisher's exact test. Changes in HR, SAP, DAP, MAP and BIS values were assessed using a two-way repeated measures analysis of variance (ANOVA). A *p*-value less than 0.05 was considered statistically significant.

3. Results

This study recruited 120 participants, 4 patients did not meet the inclusion criteria and 21 patients dropped out after randomization, leaving 95 participants to complete the study, with 48 assigned to group P and 47 to group R (Fig. 2). Patient characteristics showed no significant differences between the two groups (Table 2). As detailed in Table 3, the overall incidence of hypotension in group R was insignificantly lower than in group P (36.2% *vs.* 47.9%, $p = 0.246$). Furthermore, the occurrences of hypertension, bradycardia, and tachycardia did not significantly differ between the two groups ($p > 0.05$). In group P, three patients (6.3%) reported injection pain, whereas none did in group R ($p = 0.242$). Shivering was reported by only one patient in each group during anesthesia recovery. Notably, none of the patients experienced hypoxemia or intraoperative awareness. However, it is worth highlighting that hiccups occurred in 7 patients (14.9%) in group R during anesthesia, whereas only 1 patient (2.1%) in group P experienced hiccups during anesthesia ($p = 0.031$). Furthermore, 5 patients (71.4%) experienced hiccups during or after remimazolam injection (Table 4).

TABLE 2. Patients' characteristics.

Characteristic	Group P (n = 48)	Group R (n = 47)	*p* value
Male, n (%)	9 (18.8)	5 (10.6)	0.230
Age, years	41 (11)	43 (11)	0.464
BMI, kg/m^2	23.1 (2.8)	22.3 (2.7)	0.736
Weight, kg	60.4 (9.4)	57.4 (9.5)	0.807
Height, cm	161.3 (6.3)	160.3 (6.0)	0.750
ASA, n (%)			
I	22 (45.8)	16 (34.0)	0.241
II	26 (54.2)	31 (66.0)	
Type of surgery, n (%)			
Gynecology	36 (75.0)	32 (68.1)	
Urology	10 (20.8)	13 (27.7)	0.745
Orthopedics	2 (4.2)	2 (4.3)	

Data are n (%) and mean (SD). ASA: American Society of Anesthesiologists.

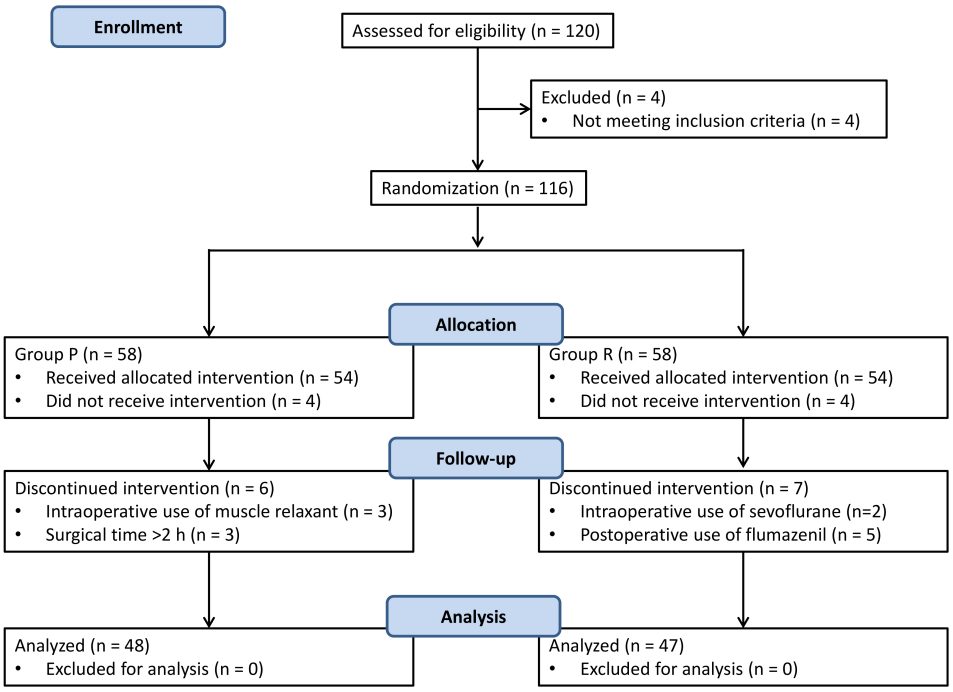

FIGURE 2. Flow diagram of the study.

TABLE 3. Adverse events.

	Group P (n = 48)	Group R (n = 47)	*p* value
Hypotension, n (%)	23 (47.9)	17 (36.2)	0.246
Post-induction hypotension, n (%)	19 (39.6)	12 (25.5)	0.144
Intraoperative hypotension, n (%)	21 (43.8)	14 (29.8)	0.158
Hypertension, n (%)	0 (0)	0 (0)	/
Bradycardia, n (%)	16 (33.3)	8 (17.0)	0.067
Post-induction bradycardia, n (%)	2 (0)	0 (0)	0.495
Intraoperative bradycardia, n (%)	16 (33.3)	8 (17.0)	0.067
Tachycardia, n (%)	0 (0)	2 (4.3)	0.242
Post-induction tachycardia, n (%)	0 (0)	2 (4.3)	0.242
Intraoperative tachycardia, n (%)	0 (0)	0 (0)	/
Injection pain, n (%)	3 (6.3)	0 (0)	0.242
Hiccup, n (%)	1 (2.1)	7 (14.9)	0.031
Hypoxemia, n (%)	0 (0)	0 (0)	/
Shivering, n (%)	1 (2.1)	1 (2.1)	1.000
Awareness, n (%)	0 (0)	0 (0)	/

Data are n (%).

Table 5 displays the first attempt LMA insertion success rate and LMA insertion score, revealing no significant differences between the two groups ($p > 0.1$). However, due to the 0.3 mg/kg bolus of remimazolam leading to a higher incidence of BIS >60, a significantly greater proportion of patients required rescue sedation in group R compared to group P (38.3% *vs.* 12.5%, $p = 0.004$). Furthermore, despite the increased need for rescue sedation, group R maintained significantly higher BIS values at T2, T3 and T4 during anesthesia induction compared to group P ($p < 0.001$, Fig. 3). Similarly, the HR in group R was significantly higher than that in group P at T2, T3, T4 and T5 ($p = 0.023$, Fig. 4A). Conversely, the changes in SAP, DAP and MAP during anesthesia induction did not exhibit significant differences between the two groups ($p > 0.1$, Fig. 4B–D). Furthermore, despite no significant disparity in operating time ($p = 0.961$, Table 5), LMA removal time was significantly prolonged in group R compared to group P (12 min *vs.* 8 min, $p = 0.001$, Table 5).

TABLE 4. Detailed information regarding patients who had hiccups.

Patients number	Group	Gender	Age (yr)	BMI (kg/m^2)	Type of surgery	Timing	Duration
1	R	Female	56	18.8	Retrograde intra-renal surgery	After remimazolam injection	5 min
2	R	Female	47	23.4	Conization of the uterine cervix	After remimazolam injection	8 min
3	R	Female	54	21.2	Bartholin gland cystectomy	After remimazolam injection	10 min
4	R	Female	52	27.1	Hysteroscopic surgery	After LMA insertion	2 min
5	R	Female	45	19.6	Hysteroscopic surgery	After remimazolam injection	8 min
6	R	Female	50	24.1	Conization of the uterine cervix	Intraoperatively	6 min
7	P	Female	58	23.5	Conization of the uterine cervix	After propofol injection	5 min
8	R	Female	60	19.4	Conization of the uterine cervix	During remimazolam injection	15 min

BMI: body mass index.

TABLE 5. Patients' clinical data.

	Group P (n = 48)	Group R (n = 47)	*p* value
First-attempt LMA insertion success rate, n (%)	45 (93.8)	42 (89.4)	0.486
LMA insertion score	6 (1)	7 (1)	0.376
Rescue sedation, n (%)	6 (12.5)	18 (38.3)	0.004
Dopamine injection, n (%)	5 (10.4)	7 (14.9)	0.511
Post-induction dopamine, n (%)	4 (8.3)	5 (10.6)	0.740
Intraoperative dopamine, n (%)	1 (2.1)	2 (4.3)	0.617
Atropine injection, n (%)	1 (2.1)	2 (4.3)	0.617
Post-induction atropine, n (%)	0 (0)	1 (2.1)	0.495
Intraoperative atropine, n (%)	1 (2.1)	1 (2.1)	1.000
Intraoperative sufentanil, n (%)	4 (8.3)	5 (10.6)	0.740
Surgical time (min)	40 (23)	38 (23)	0.961
LMA removal time (min)	8 (5)	12 (7)	0.001

Data are n (%) and mean (SD). LMA: Laryngeal mask airway.

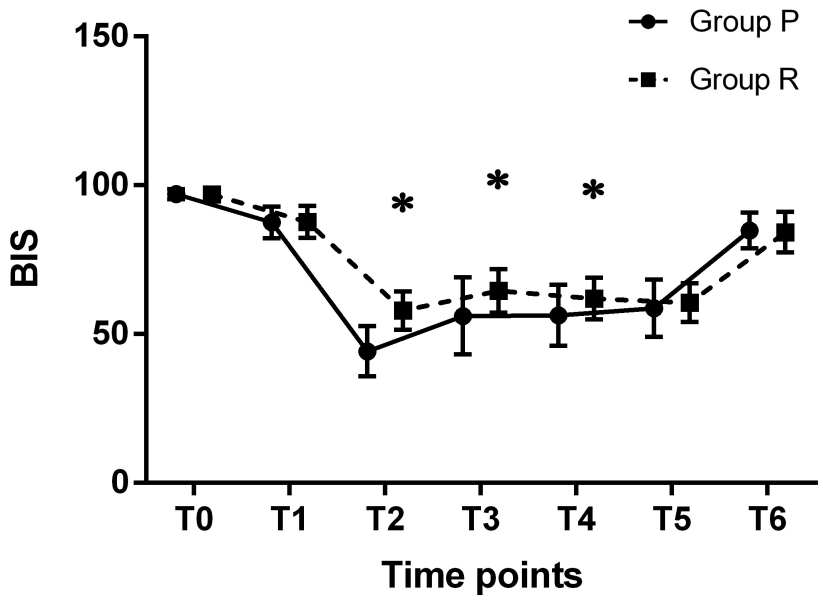

FIGURE 3. BIS changes during anesthesia induction and LMA insertion. Data are mean with standard deviation. *$p <$ 0.05 compared to group P at the same time points. BIS: bispectral index.

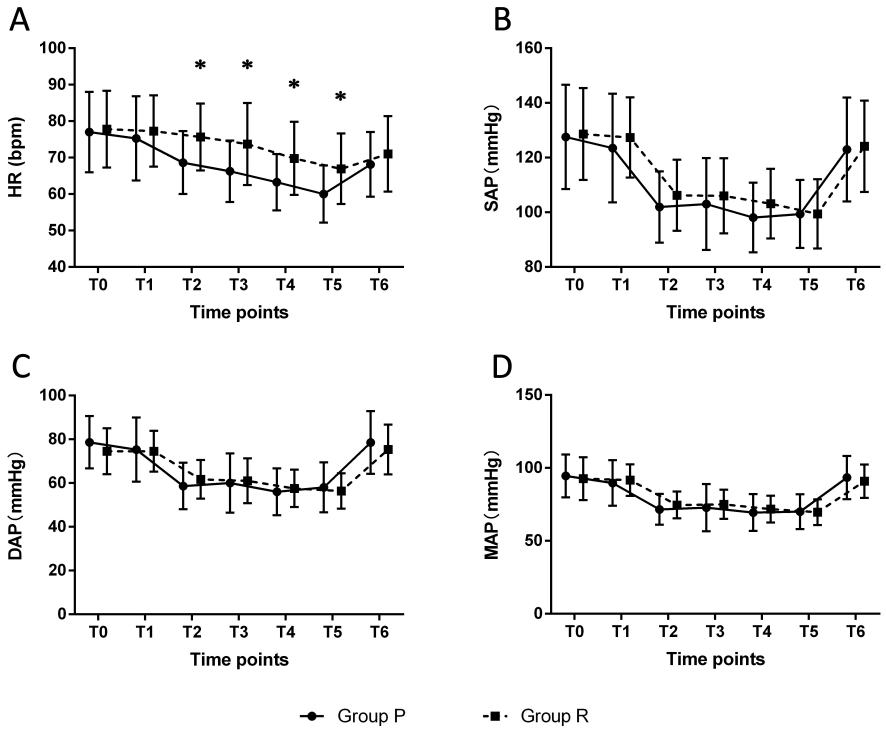

FIGURE 4. Blood pressure and HR changes during anesthesia induction and LMA insertion and 2 min after LMA removal. Data are mean with standard deviation. *$p < 0.05$ compared to group P at the same time points. T0: immediately before sufentanil administration, T1: 3 min after sufentanil administration, T2: immediately before the first attempt of LMA insertion, T3: immediately after successful LMA insertion, T4: 2 min after LMA insertion, T5: 4 min after LMA insertion, T6: 2 min after LMA removal. HR: heart rates; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure.

4. Discussion

Previous studies have shown that the main advantage of remimazolam over propofol is that it has less of an effect on blood pressure [4, 5, 9]. However, in this study, we found a slightly but insignificantly lower incidence of hypotension with remimazolam compared with propofol in LMA anesthesia without muscle relaxants. We hypothesize this lack of statistical significance to the relatively small sample size and the use of a relatively higher dose of remimazolam in the context of LMA anesthesia during surgeries without muscle relaxants. Furthermore, our findings also indicated that remimazolam administration was associated with a higher occurrence of hiccups following anesthesia induction, and the time required for LMA removal was longer after remimazolam anesthesia compared to anesthesia using propofol.

The dose of remimazolam administered to patients can impact their blood pressure, and in our study, the initial induction dose of remimazolam was 0.3 mg/kg. In a study by Dai *et al.* [10], where sufentanil and cisatracurium were used for anesthesia induction and tracheal intubation, the incidence of hypotension induced by remimazolam bolus doses of 0.2, 0.3 and 0.4 mg/kg were found to be 13%, 24% and 34%, respectively. In our study, we observed an incidence of hypotension during anesthesia induction with remimazolam 0.3 mg/kg to be 25.5%, which aligns with previous findings. However, Dai *et al.* [10] also reported that the MAP during anesthesia induction with 0.3 mg/kg remimazolam was significantly higher than with propofol. Similarly, in a study by Tang *et al.* [7], using remifentanil and sufentanil in combination with remimazolam at a total induction dose of 0.3 mg/kg, they found that it provided similar LMA insertion conditions without muscle relaxants compared to propofol. Furthermore, the SAP immediately following LMA insertion was slightly but significantly lower with remimazolam than with propofol (n = 36). In contrast, despite the larger sample size in our study (n = 48 and n = 47), we did not observe significant differences in blood pressure between the two groups. We believe that the higher incidence of rescue sedation required to achieve the target BIS value during anesthesia induction and LMA insertion in group R compared to group P (38.3% *vs.* 12.5%) may have contributed to the lack of significance in blood pressure values.

In this study, despite the higher incidence of rescue sedation, the BIS value during the induction of anesthesia was still significantly higher in group R compared to group P. The relationship between the depth of remimazolam anesthesia and BIS remains unclear [8], prompting the decision to proceed with LMA insertion when patients were unresponsive to verbal contact or jaw thrust even after rescue sedation. However, it is important to note that remimazolam anesthesia offered a more stable HR compared to propofol anesthesia, which may be attributed to less vagal stimulation and a shallower depth of anesthesia achieved with remimazolam as opposed to propofol.

Furthermore, only three patients experienced injection pain during propofol injection, resulting in an incidence of 6.3%,

which was notably lower than previously reported rates (up to 80.5%) [5]. We attribute this lower incidence to the analgesic effect of sufentanil administered prior to propofol injection. Although the operative time was similar between the two groups, LMA removal took longer under remimazolam anesthesia compared to propofol anesthesia, consistent with findings from prior studies [4, 5]. Remimazolam sedation can be rapidly reversed by flumazenil within 2 minutes [4], allowing for rapid recovery from remimazolam anesthesia. However, Oh *et al.* [11] reported that when a large dose of remimazolam was administered intraoperatively, there might be a rebound increase in remimazolam concentration after flumazenil reversal, potentially leading to re-sedation in patients.

Notably, the incidence of hiccups in group R was 14.9%, which was significantly higher than in group P. Interestingly, two patients in group R experienced hiccups for more than 10 minutes, although the hiccups were typically self-limiting. Hiccups can be triggered by stimulation of the vagus nerve or phrenic nerve, with the vagus nerve innervating the pharynx and upper esophagus. Previous studies have indicated that LMA insertion can stimulate the hypopharynx and induce hiccups, with reported incidences ranging from 3% to 11% [12, 13]. However, in our study, only one patient experienced hiccups after LMA insertion, while five patients experienced hiccups during or after the bolus administration of remimazolam. Therefore, it is plausible that a rapid bolus of remimazolam as part of the induction dose may contribute to hiccups. It is worth noting that remimazolam-induced hiccups have been rarely reported in previous studies. Chen *et al.* [14] mentioned that hiccups occurred "frequently" in patients receiving intravenous remimazolam at a dose of 0.4 mg/kg over 1 minute, followed by an infusion at 1.5 mg/kg/h. This bolus dose of 0.4 mg/kg was higher than the generally recommended dose of 0.1 to 0.2 mg/kg over 1 minute [4, 5]. However, their study did not provide detailed information about the hiccups. Another study by Dai *et al.* [10] reported that remimazolam administered at a dose of 0.4 mg/kg over 1 minute successfully and safely induced anesthesia, but hiccups were not mentioned. We contacted the authors through correspondence, and they confirmed that few patients experienced hiccups [15].

The exact mechanism behind remimazolam-induced hiccups remains unclear, and the duration of hiccups appears unpredictable. We believe that the primary risk factor contributing to the high incidence of remimazolam-induced hiccups in our study was the rapid administration of 0.3 mg/kg of remimazolam within 30 seconds, resulting in a transient spike in plasma remimazolam concentration. A similar observation was made by Tang *et al.* [7], who reported that 11.1% (4 out of 36) of patients experienced hiccups during the induction of anesthesia and LMA insertion without muscle relaxants when administered 0.3 mg/kg of remimazolam. However, their study involved administering the total remimazolam dose in two boluses, and they did not specify the timing of the hiccups. Interestingly, Oh *et al.* [16] conducted a research to find the effective dose of remimazolam co-administered with remifentanil to facilitate LMA insertion without muscle relaxant, the authors administered remimazolam (0.15 mg/kg to 0.45 mg/kg) over few seconds and 2 out of 25 patients had hiccups. In contrast, Choi *et al.* [17] infused remimazolam at a dose of 12 mg/kg/h (0.2 mg/kg/min) for anesthesia induction and LMA insertion with remifentanil, no hiccups were reported in their study.

Notably, midazolam, a commonly used benzodiazepine for anesthesia, has also been reported to induce hiccups. For instance, Marhofer *et al.* [18] reported that the incidence of rectal midazolam-induced hiccups in children ranged from 22% to 26%, and these hiccups were effectively terminated by intranasal ethyl chloride spray. Liu *et al.* [19] documented that during gastrointestinal endoscopy and colonoscopy procedures, hiccups occurred more frequently in patients who received sedation compared to those without sedation. Moreover, hiccups were more common in patients who received a higher dose (2 mg) of midazolam than in those who received 1 mg. The authors suggested that midazolam might affect diaphragm contractility, leading to hiccups. Additionally, there have been reports of midazolam-induced hiccups being successfully treated with flumazenil [20]. Consequently, it is conceivable that the gamma-aminobutyric acid (GABA) receptor may play a role in benzodiazepine-induced hiccups. However, it is worth noting that there have been cases of hiccups treated with midazolam as well [21, 22]. Given the findings of this study, clinicians should exercise caution regarding this adverse effect of remimazolam and avoid rapid bolus administration, especially in cases of remimazolam anesthesia without muscle relaxants.

5. Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small, which might explain the lack of significant differences in the incidence of hypotension between remimazolam and propofol-based LMA anesthesia without muscle relaxants. Second, we did not follow certain recommended remimazolam infusion rates, such as 12 mg/kg/h for anesthesia induction. Therefore, the study does not provide insights into potential differences between bolus injection and continuous infusion of remimazolam for anesthesia induction and LMA insertion without muscle relaxants. Third, we used a sufentanil induction dose of 0.2 μg/kg, and it could be possible that different hemodynamic changes could occur with higher sufentanil doses, potentially leading to different outcomes in propofol and remimazolam anesthesia for LMA insertion without muscle relaxants. Further research with larger sample sizes and different dosing regimens is needed to better understand these aspects.

6. Conclusions

Our study did not reveal a statistically significant difference in the incidence of hypotension during LMA anesthesia without muscle relaxants when comparing the use of remimazolam to propofol, possibly due to the limited sample size. Considering the risk of remimazolam-induced hiccups associated with rapid bolus administration, a larger-scale study with similar conditions might not be feasible. Furthermore, we observed higher BIS values during the induction of anesthesia with remimazolam compared to propofol, but remimazolam provided more stable heart rates, with slightly longer recovery times

compared to propofol. Additional research with larger sample sizes and optimized dosing protocols is needed to gain a more comprehensive understanding of the comparative effects of these two agents in LMA anesthesia without muscle relaxants.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

QH, YZ and GYK—designed the research study, analyzed the data. QH, YZ, WYC, KL, TH, BBP and YZL—performed the research. QH and YZ—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research protocol was approved by the Ethics Committee of Hunan Provincial People's Hospital (Approval No. 2020-31) and was registered with the Chinese Clinical Trial Registry (ChiCTR 2000037276). All patients have signed informed consent for the study.

ACKNOWLEDGMENT

Not applicable.

FUNDING

Health Commission of Hunan Province (202104111828); Beijing Medical Award Foundation (H2020-28, H2021-24).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Qian Huang, Yi Zou, Wenyan Chen, Ke Liu, Tao Hu, Bingbing Pan, *et al*. Comparison of remimazolam tosylate and propofol in patients undergoing general anesthesia using a laryngeal mask airway without muscle relaxants. Signa Vitae. 2024; 20(3): 63-70. doi: 10.22514/sv.2024.029.