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Effects of remimazolam, cipepofol and propofol on circulation during induction period of general anesthesia

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Abstract: Objective To observe the effects of remimazolam, cipepofol, and propofol on hemodynamics, blood glucose, and lactate levels during general anesthesia induction. **Methods** A total of 126 elective surgery patients at the Second Affiliated Hospital of Nanjing Medical University from August to November 2023, undergoing non-cardiothoracic and neurosurgical procedures under general anesthesia, were included. Patients were randomly assigned using a random number table into three groups: remimazolam group, cipepofol group, and propofol group, with 42 patients in each group. Anesthesia induction included intravenous fentanyl 0.2-0.3 μg/kg followed by administration of the study drugs: remimazolam group received remimazolam 0.3 mg/kg, cipepofol group received cipepofol 0.4 mg/kg (0.3 mg/kg for patients over 70 years), and propofol group received propofol 2.0 mg/kg (1.5 mg/kg for patients over 70 years). Rocuronium 0.6 mg/kg was injected after loss of eyelash reflex, followed by placement of a laryngeal mask for controlled ventilation. Heart rate (HR), mean arterial pressure (MAP), and bispectral index (BIS) values were recorded at upon entry (T_0), before intubation (T_1), immediately after intubation (T_2), and 3 minutes after intubation (T_3). Blood glucose and lactate levels were recorded at T_1 and T_3. Incidence of injection pain, hypotension, bradycardia, hiccup, agitation during emergence, patient satisfaction upon leaving the recovery room, intraoperative awareness, postoperative dizziness, nausea, and vomiting were also documented. **Results** A total of 42 cases were included in the remimazolam group, 36 cases in the cipepofol group, and 39 cases in the propofol group. The incidence of hypotension during induction was 9 cases (21%) in the remimazolam group, 15 cases (42%) in the cipepofol group, and 21 cases (54%) in the propofol group, and the difference among three groups was significant (χ^2=9.204, P=0.010). The remimazolam group had a significantly lower incidence of hypotension compared to the propofol group (P<0.017). Bradycardia during induction occurred in 6 cases (14%) in the remimazolam group, 18 cases (50%) in the cipepofol group, and 12 cases (31%) in the propofol group, with statistically significant differences among the groups (χ^2=11.607, P=0.003). The remimazolam group had a significantly lower incidence of bradycardia compared to the cipepofol group(P<0.017). Multivariate analysis indicated that the remimazolam was an independent protective factor against hypotension (OR=0.199, 95%CI:0.073-0.549, P=0.002) and bradycardia (OR=0.173,95%CI:0.047-0.520, P=0.002) during induction. There was statistically significant difference in the incidence of injection pain among the remimazolam group, cipepofol group, and propofol group (14% *vs* 0 *vs* 54%, χ^2=33.429, P<0.001). **Conclusion** Remimazolam, cipepofol, and propofol can be used for anesthesia induction. Propofol could significantly induce hypotension, while propofol notably induces bradycardia. Remimazolam acts as an independent protective factor against hypotension and bradycardia during induction.

Keywords: Cipepofol; Remimazolam; Propofol; Induction; Circulatory suppression; Injection pain; Hypotension; Bradycardia; Mean arterial pressure

Propofol is the most commonly used classic intravenous anesthetic in clinical practice. It acts quickly and has a rapid recovery time, but it also has significant side effects, such as respiratory and circulatory suppression, and injection pain [1]. In recent years, the advent of new drugs such as remimazolam and cipepofol has challenged propofol's status as a first-line agent. Current research mainly focuses on clinical comparisons between two drugs, such as cipepofol *vs.* propofol [1-2] and remimazolam *vs.* propofol [3]. However, there are few experimental designs that directly compare all three drugs in the same study. This study aims to observe the effects of remimazolam, cipepofol, and propofol on circulation and stress during the induction phase of general anesthesia, providing scientific evidence for the optimal clinical use of these drugs.

1 Materials and Methods

1.1 General Data

A total of 126 patients who underwent elective non-cardiothoracic and neurosurgical procedures under general anesthesia at the Second Affiliated Hospital of Nanjing Medical University between August and November 2023

were selected. Inclusion criteria: Age 18-78 years, any gender; American Society of Anesthesiologists (ASA) physical status classification I-III; Body Mass Index (BMI) between 18.50 and 29.90 kg/m². The study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University (2023-KY-156-01), and informed consent was obtained from all patients and their families. Exclusion criteria: Severe liver and kidney dysfunction, severe cardiopulmonary insufficiency, poorly controlled hypertension and hyperglycemia, central nervous system diseases, allergy to anesthetics, and a history of substance abuse. Patients were randomly divided into three groups based on a random number table: remimazolam group, cipepofol group, and propofol group, with 42 patients in each group.

1.2 Anesthesia Method

All patients were instructed to fast for 6 hours and avoid drinking for 2 hours prior to surgery. Upon entering the operating room, patients were positioned supine and monitored with electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and bispectral index (BIS). A peripheral intravenous line was established. Anesthesia induction: After sufficient denitrogenation and oxygenation, all patients received an intravenous injection of sufentanil 0.2-0.3 μg/kg. The respective study drug was injected for each group: remimazolam group received remimazolam 0.3 mg/kg; cipepofol group received cipepofol 0.4 mg/kg (0.3 mg/kg for patients over 70 years); propofol group received propofol 2.0 mg/kg (1.5 mg/kg for patients over 70 years). After disappearance of the corneal reflex, rocuronium 0.6 mg/kg was injected, and after 3 minutes, a laryngeal mask was placed, followed by controlled ventilation with a tidal volume of 6-8 mL/kg, a respiratory rate of 10-12 breaths per minute, and an inspiratory-expiratory ratio of 1:2. End-expiratory CO_2 pressure was maintained at 35-45 mmHg. All three groups were maintained on a combination of intravenous and inhalation anesthesia, with sevoflurane 1%–3%, propofol infusion 4-12 $mg \cdot kg^{-1} \cdot h^{-1}$, remifentanil 8-15 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and intermittent bolus of rocuronium 0.1 mg/kg. BIS was maintained between 40 and 60. Heart rate and MAP were kept within ±20% of baseline values. After surgery, once patients had regained consciousness, the laryngeal mask was removed, and they were transferred to the post-anesthesia care unit.

1.3 Observation Indicators

Patient general information, time for the disappearance of the corneal reflex, successful sedation rate, initial laryngeal mask insertion success rate, and use of vasoactive drugs during induction were recorded. MAP, HR, and BIS values were recorded at the following time points: immediately upon entering the operating room (T_0), before intubation (T_1), immediately after intubation (T_2), and 3 minutes after intubation (T_3). Blood glucose and lactate levels at T_1 and T_3 were also recorded. Injection pain (rated 0-3: no pain, mild, moderate, severe), hypotension (drop >30% of baseline), bradycardia (drop >20% of baseline), hiccups, and post-operative agitation were noted. Patient satisfaction and the presence of intraoperative awareness, dizziness, nausea, and vomiting were also recorded after leaving the recovery room.

1.4 Statistical Methods

All statistical analyses were performed using Stata 17.0. Normally distributed continuous data are presented as $\bar{x} \pm s$, and comparisons between groups were made using ANOVA. Skewed data are presented as *M*(*IQR*) and compared using the Kruskal-Wallis test. Categorical data are expressed as frequency (%), with comparisons made using the chi-square test. Ordinal data were analyzed using the rank sum test. Multivariate analysis was conducted using logistic regression for binary outcomes, with Wald tests for significance. Repeated measures data were compared using linear mixed models, and group differences were estimated using the maximum likelihood method. Bonferroni correction was applied for pairwise comparisons of continuous data, and the chi-square test for categorical data. $P<0.05$ was considered that the difference was statistically significant.

2 Results

2.1 General Data

A total of 126 patients were initially screened, and 117 patients were ultimately included in the study: 42 patients in the remimazolam group, 36 in the cipepofol group, and 39 in the propofol group. Exclusion reasons included: 1 case of antibiotic allergy, 2 cases where the surgery was postponed, and 6 cases with incomplete data collection. There were no statistically significant differences in the general characteristics of the three groups ($P>0.05$), as shown in **Table 1**.

Tab. 1 Comparison of general conditions among three groups of patients

Group	Cases	Male/Female (case)	Age (years, $\bar{x} \pm s$)	BMI (kg/m², $\bar{x} \pm s$)	ASA(case, Ⅰ/Ⅱ/Ⅲ)	Surgery time[min, *M*(*IQR*)]
Remimazolam group	42	36/6	60.70±15.00	24.40±2.90	3/30/9	47.5(55)
Cipepofol group	36	24/12	59.90±10.80	23.50±3.50	0/30/6	45(70)
Propofol group	39	27/12	60.50±12.60	24.00±2.90	6/27/6	40(15)
$\chi^2/F/Z$ **value**		4.496	0.040	0.800	2.271	0.328
P **value**		0.106	0.962	0.454	0.321	0.849

2.2 Induction Phase Main Indicators

Induction was successful in all groups. The univariate comparison of the main induction phase indicators is shown in **Table 2**. The remimazolam group had the lowest

rates of hypotension, bradycardia, and use of vasoactive drugs (P<0.05). Multivariate analysis showed that remimazolam was an independent protective factor for hypotension (OR=0.207, 95%CI: 0.074–0.582, P=0.003) and bradycardia (OR=0.196, 95%CI: 0.065–0.593, P=0.004), as shown in **Table 3** and **Table 4**.

Tab. 2 Comparison of main indicators during induction period among three groups of patients [case (%)]

Group	Cases	Eyelash reflex vanish (s, $\bar{x}$ ±s)	First successful laryngeal mask	Hypotension	Low heart rate	Use of vasoactive drugs
Remimazolam group	42	49.90±14.90	33(79)	9(21)[a]	6(14)[a]	6(14)
Cipepofol group	36	50.80±16.40	33(92)	15(42)	18(50)	12(33)
Propofol group	39	45.70±12.00	36(92)	21(54)	12(31)	15(38)
χ^2/F value		1.370	4.351	9.204	11.607	6.512
***P* value**		0.258	0.114	0.009	0.003	0.039

Note: Compared with Propofol group, [a]P<0.017.

Tab. 3 Logistic regression analysis of risk factors associated with hypotension during induction

Indicators	*β*	*SE*	*OR*	*P* value	95%*CI*
Group					
Cipepofol	-0.496	0.479	0.609	0.301	0.238-1.559
Remimazolam	-1.612	0.516	0.199	0.002	0.073-0.549
Propofol	1				
Gender					
Male	1				
Female	-0.792	0.499	0.440	0.113	0.170-1.206
ASA grading					
I+II	1				
III	-0.333	0.559	0.221	0.552	0.239-2.147
Age	-0.016	0.016	0.990	0.324	0.953-1.016
BMI	0.010	0.068	1.044	0.882	0.885-1.153

Tab.4 Logistic regression analysis of risk factors associated with low heart rate during induction

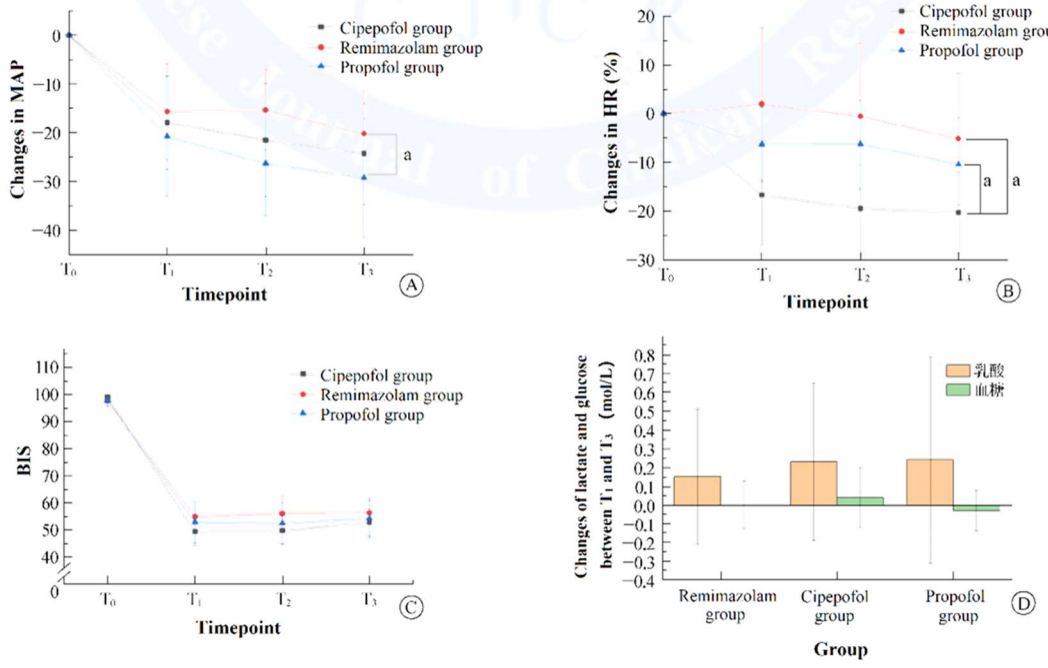
Indicators	*β*	*SE*	*OR*	*P* value	95%*CI*
Group					
Cipepofol	1				
Remimazolam	-1.757	0.563	0.173	0.002	0.057-0.520
Propofol	-0.827	0.485	0.437	0.088	0.169-1.132
Gender					
Male	1				
Female	0.371	0.483	1.449	0.442	0.562-3.735
ASA grading					
I+II	1				
III	-0.110	0.574	0.896	0.848	0.291-2.759
Age	0.009	0.018	1.009	0.603	0.974-1.045
BMI	0.023	0.069	1.023	0.741	0.894-1.171

2.3 Other Induction Phase Indicators

The changes in BIS values, HR, and MAP at T_0 to T_3, as well as the differences in blood lactate and glucose levels at T_1 and T_3, were recorded and compared. As shown in **Figure 1,** there was no significant difference in BIS values among the three groups (P>0.05). The differences in MAP (likelihood ratio χ^2=14.080, P=0.001) and HR (likelihood ratio χ^2=41.690, P<0.01). There was no statistically significant difference in blood lactate and blood glucose levels among three groups (P>0.05).

2.4 Adverse Reactions

Injection pain during induction occurred in 6 patients (14%) in the remimazolam group, all of whom had moderate pain. No injection pain was reported in the cipepofol group, whereas 21 patients (54%) in the propofol group experienced pain, with 9 reporting mild pain, 9 moderate, and 3 severe. The incidence of injection pain differed significantly between the groups (χ^2=33.429, P<0.01). The incidence of injection pain in the propofol group was significantly higher than in both the remimazolam group and cipepofol group (P<0.017). However, no significant difference was observed between the remimazolam group and cipepofol group (P>0.017). There was no case of hiccups, intraoperative awareness, post-operative agitation, dizziness, or nausea/vomiting in any group. Patient satisfaction was 100% in all three groups.



3 Discussion

Anesthesia induction marks the beginning of clinical anesthesia, during which the patient transitions from a wakeful state to anesthesia. During this phase, significant changes occur in various body systems. Successful anesthesia induction should be safe, smooth, and comfortable, and it is closely related to the choice of induction drugs. Currently, commonly used anesthesia induction drugs include the classic propofol, the new drug independently developed by China — cipepofol, and remimazolam, a new soft drug that combines the advantages of sufentanil and midazolam. This study compared the effects of these three drugs in clinical anesthesia induction to provide more evidence for clinical drug selection.

In this study, all three drugs used for anesthesia induction were safe, effective, and fast, without the need for additional rescue medications. All three drugs could cause hypotension after anesthesia induction, with propofol causing the most significant hypotensive effect, etomidate having a slightly weaker effect, and remimazolam having the least impact on blood pressure. The rapid and significant hypotensive effect of propofol is related to its dual mechanism of suppressing myocardial activity and reducing systemic vascular resistance [1]. Etomidate showed similar hypotensive effects to propofol [4], although this contrasts with some previous studies [2, 5-6]. This difference is likely due to the choice of etomidate induction dose in this study (0.4 mg/kg). Duan *et al.* [7] found that 0.3 mg/kg of etomidate used for anesthesia induction resulted in the lowest incidence of adverse events. In healthy volunteers, the effects of etomidate and propofol on acute hemodynamics were shown to have no difference in their impact on MAP within 5 minutes after anesthesia induction [4], which is consistent with our findings. The hypotensive effect of remimazolam was significantly weaker than that of propofol, with fewer vasopressor requirements, which may be attributed to the ability of remimazolam to better maintain systemic vascular resistance [3]. It is noteworthy that the highest incidence of hypotension occurred at the T_3 time point for all three groups, suggesting that laryngeal mask insertion causes less stimulation [6], and that adjusting the drug induction dose or changing the administration method (e.g., target-controlled infusion of propofol) may help mitigate this. Clinically, attention should be given to the risk of hypotension during the period from anesthesia induction to the start of surgery, with increased monitoring, timely fluid supplementation, and vasopressor administration.

All three drugs also caused bradycardia after anesthesia induction, with etomidate significantly lowering heart rate (appearing earlier and to a greater extent). The reduction in heart rate leads to a decrease in cardiac output, which in turn causes blood pressure to drop. Therefore, it is speculated that the hypotension observed after etomidate induction is related to its effect on heart rate. Hasegawa *et al.* [8] found that both propofol and remimazolam reduced autonomic nervous system activity during anesthesia induction, with remimazolam maintaining a balance between sympathetic and parasympathetic activity, while propofol shifted the balance towards sympathetic dominance. In this study, the bradycardic effect of propofol and remimazolam was weaker than that of etomidate, suggesting that the mechanisms through which etomidate affects the autonomic nervous system may differ from those of propofol and remimazolam, warranting further research. Additionally, we found that the bradycardic effect of propofol was weaker than its hypotensive effect, which may be related to the dominance of sympathetic nervous system activity after propofol induction.

Ko *et al.* [9] found that the anesthetic depth induced by remimazolam was shallower than that induced by propofol. Chen *et al.* [6] found that the BIS values induced by etomidate were significantly lower than those induced by propofol. In this study, although no statistically significant differences in BIS values were observed at any time point, the trends were consistent with these previous findings. This suggests that (1) there may indeed be differences in anesthetic depth between the three drugs, and (2) the correlation between remimazolam's sedative effect and BIS values is weaker than that of the other two drugs [10-11]. Furthermore, the peak sedative effect of remimazolam lagged behind that of cipepofol and propofol, and its plasma half-life was longer than that of the other two drugs [12], which may explain why the first-pass success rate of laryngeal mask insertion was slightly lower in the remimazolam group compared to the cipepofol group and propofol group. However, the lower first-pass success rate of laryngeal mask insertion in the remimazolam group may also be related to its weaker inhibitory effect on the pharyngeal reflex [13].

Compared with cipepofol and propofol, remimazolam induced less blood glucose fluctuation, though this difference was not statistically significant. Wu *et al*. [14] found that 0.2 mg/kg remimazolam could inhibit the stress response during general anesthesia induction in patients undergoing laparoscopic cholecystectomy. Zhao *et al.* [15] also found that remimazolam (0.3 mg/kg) could suppress the stress response in patients undergoing hysteroscopic surgery under general anesthesia. This may be related to the ability of benzodiazepines to suppress the secretion of adrenocorticotropic hormone and cortisol during stress, and possibly to the more stable heart rate (HR) and MAP maintained by remimazolam during induction [16]. In addition, all three drugs had minimal effects on blood lactate levels.

In conclusion, remimazolam, cipepofol, and propofol can all be successfully used for anesthesia induction. Remimazolam provides the most stable hemodynamics, propofol has the most significant hypotensive effect, and cipepofol causes the most pronounced bradycardia. Both remimazolam and cipepofol have almost no injection pain. The choice of drug should be based on surgery, anesthesia plan, anesthesiologist’s preferences, and patient’s condition, with enhanced monitoring throughout the procedure.

Conflicts of Interest None

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·论　著·

瑞马唑仑与环泊酚及丙泊酚在全麻诱导期对循环的影响

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摘要：目的　观察瑞马唑仑、环泊酚及丙泊酚用于全麻诱导时对患者血流动力学及血糖和乳酸的影响。**方法**　选择 2023 年 8 月至 11 月南京医科大学第二附属医院全麻下行非心胸外科及神经外科的择期手术患者 126 例。依据随机数字表法，将患者分为瑞马唑仑组、环泊酚组和丙泊酚组，每组 42 例。全麻诱导（静脉注射舒芬太尼 0.2～0.3 μg/kg）后，三组分别注射研究药物：瑞马唑仑组静脉注射瑞马唑仑 0.3 mg/kg，环泊酚组静脉注射环泊酚 0.4 mg/kg（70 岁以上为 0.3 mg/kg），丙泊酚组静脉注射丙泊酚 2.0 mg/kg（70 岁以上为 1.5 mg/kg）。待患者睫毛反射消失，注射罗库溴铵 0.6 mg/kg，3 min 后置入喉罩，行呼吸控制。记录患者入室后（T_0）、插管前（T_1）、插管后即刻（T_2）、插管后 3 min（T_3）的心率（HR）、平均动脉压（MAP）及脑电双频指数（BIS）值；记录 T_1、T_3 的血糖及乳酸值；记录诱导期注射痛、低血压、低心率、呃逆、苏醒期躁动等发生情况；记录出复苏室时患者满意度及有无术中知晓、头晕、恶心呕吐等不良反应。**结果**　最终纳入瑞马唑仑组 42 例、环泊酚组 36 例、丙泊酚组 39 例。诱导期低血压发生情况为瑞马唑仑组 9 例（21%），环泊酚组 15 例（42%），丙泊酚组 21 例（54%），三组间差异有统计学意义（$\chi^2=9.204$，$P=0.010$），且瑞马唑仑组低血压发生率显著低于丙泊酚组（$P<0.017$）。诱导期低心率瑞马唑仑组 6 例（14%），环泊酚组 18 例（50%），丙泊酚组 12 例（31%），三组间差异有统计学意义（$\chi^2=11.607$，$P=0.003$），且瑞马唑仑组低心率发生率显著低于环泊酚组（$P<0.017$）。多因素分析结果显示瑞马唑仑是诱导期低血压（$OR=1.199$，95%CI：0.073～0.549，$P=0.002$）和低心率（$OR=0.173$，95%CI：0.057～0.520，$P=0.002$）的独立保护因素。瑞马唑仑组、环泊酚组和丙泊酚组注射痛发生率差异有统计学意义（14% *vs* 0 *vs* 54%，$\chi^2=33.429$，$P<0.001$）。**结论**　瑞马唑仑、环泊酚及丙泊酚均可用于麻醉诱导。丙泊酚低血压作用显著，环泊酚低心率作用明显，瑞马唑仑是诱导期低血压和低心率的独立性保护因素。

关键词：环泊酚；瑞马唑仑；丙泊酚；麻醉诱导；循环抑制；注射痛；低血压；低心率；平均动脉压
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Abstract: Objective　To observe the effects of remimazolam, cipepofol, and propofol on hemodynamics, blood glucose, and lactate levels during general anesthesia induction. **Methods**　A total of 126 elective surgery patients at the Second Affiliated Hospital of Nanjing Medical University from August to November 2023, undergoing non-cardiothoracic and neurosurgical procedures under general anesthesia, were included. Patients were randomly assigned using a random number table into three groups: remimazolam group, cipepofol group, and propofol group, with 42 patients in each group. Anesthesia induction included intravenous sufentanil 0.2-0.3 μg/kg followed by administration of the study drugs: remimazolam group received remimazolam 0.3 mg/kg, cipepofol group received cipepofol 0.4 mg/kg (0.3 mg/kg for patients over 70 years), and propofol group received propofol 2.0 mg/kg (1.5 mg/kg for patients over 70 years).

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Rocuronium 0.6 mg/kg was injected after loss of eyelash reflex, followed by placement of a laryngeal mask for ventilation control. Heart rate (HR), mean arterial pressure (MAP), and bispectral index (BIS) values were recorded at upon entry (T_0), before intubation (T_1), immediately after intubation (T_2), and 3 minutes after intubation (T_3). Blood glucose and lactate levels were recorded at T_1 and T_3. Incidence of injection pain, hypotension, bradycardia, hiccup, agitation during emergence, patient satisfaction upon leaving the recovery room, intraoperative awareness, postoperative dizziness, nausea, and vomiting were also documented. **Results** A total of 42 cases were included in the remimazolam group, 36 cases in the cipepofol group, and 39 cases in the propofol group. The incidence of hypotension during induction was 9 cases (21%) in the remimazolam group, 15 cases (42%) in the cipepofol group, and 21 cases (54%) in the propofol group, and the difference among three groups was significant ($\chi^2=9.204$, $P=0.010$). The remimazolam group had a significantly lower incidence of hypotension compared to the propofol group ($P<0.017$). Bradycardia during induction occurred in 6 cases (14%) in the remimazolam group, 18 cases (50%) in the cipepofol group, and 12 cases (31%) in the propofol group, with significant difference among three groups ($\chi^2=11.607$, $P=0.003$). The remimazolam group had a significantly lower incidence of bradycardia compared to the cipepofol group ($P<0.017$). Multivariate analysis indicated that the remimazolam was an independent protective factor against hypotension ($OR=0.199$, 95%CI: 0.073-0.549, $P=0.002$) and bradycardia ($OR=0.173$, 95%CI: 0.057-0.520, $P=0.002$) during induction. There was statistically significant difference in the incidence of injection pain among the remimazolam group, cipepofol group, and propofol group (14% *vs* 0 *vs* 54%, $\chi^2=33.429$, $P<0.001$). **Conclusion** Remimazolam, cipepofol, and propofol can be used for anesthesia induction. Propofol could induce hypotension, while propofol notably induces bradycardia. Remimazolam acts as an independent protective factor against hypotension and bradycardia during induction.

Keywords: Cipepofol; Remimazolam; Propofol; Induction; Circulatory suppression; Injection pain; Hypotension; Bradycardia; Mean arterial pressure

丙泊酚是目前临床使用最多的经典静脉麻醉药，起效快、苏醒快，但也存在显著的呼吸循环抑制、注射痛等副作用[1]。近年来随着新药环泊酚、瑞马唑仑的问世，丙泊酚的一线地位受到了挑战。目前研究多集中在两种药物如环泊酚与丙泊酚[1-2]、瑞马唑仑与丙泊酚[3]的临床应用比较，将三药纳入同一研究进行直观对比的试验设计还很少。本研究旨在观察瑞马唑仑、环泊酚及丙泊酚在全麻诱导期对循环及应激的影响，为临床最佳用药提供参考依据。

1　资料与方法

1.1　*一般资料*　选择 2023 年 8 月至 11 月南京医科大学第二附属医院全麻下行非心胸外科及神经外科的择期手术患者 126 例。纳入标准：年龄 18~78 岁，性别不限；美国麻醉医师协会（American Society of Anesthesiologists, ASA）分级为Ⅰ~Ⅲ级；身体质量指数（body mass index, BMI）18.50~29.90 kg/m^2。研究已获南京医科大学第二附属医院伦理委员会批准（2023-KY-156-01），均获得患者及家属知情同意。排除标准：严重肝肾功能不全、严重心肺功能不全、高血压及高血糖控制不佳、中枢神经系统疾病、麻醉药过敏史及药物滥用史者。依据随机数字表法，将患者分为瑞马唑仑组、环泊酚组和丙泊酚组，每组 42 例。

1.2　*麻醉方法*　所有患者术前禁食 6 h、禁饮 2 h。入手术室后平卧，行心电监护，对心率（heart rate, HR）、平均动脉压（mean arterial pressure, MAP）、脉搏血氧饱和度（saturation of perpheral oxygen, SpO_2）及脑电双频指数（bispectral index, BIS）监测，开放外周静脉通路。麻醉诱导：所有患者充分去氮给氧后，静脉注射舒芬太尼 0.2~0.3 μg/kg，三组分别注射研究药物，瑞马唑仑组静脉注射瑞马唑仑 0.3 mg/kg；环泊酚组静脉注射环泊酚 0.4 mg/kg（70 岁以上为 0.3 mg/kg）；丙泊酚组静脉注射丙泊酚 2.0 mg/kg（70 岁以上为 1.5 mg/kg）。待患者睫毛反射消失，注射罗库溴铵 0.6 mg/kg，3 min 后置入喉罩，行呼吸控制，潮气量 6~8 mL/L，呼吸频率 10~12 次/min，吸呼比 1∶2，维持呼气末二氧化碳分压 35~45 mmHg。三组患者均采用静吸复合麻醉维持，吸入七氟烷 1%~3%，泵注丙泊酚 4~12 mg·kg^{-1}·h^{-1}，瑞芬太尼 8~15 μg·kg^{-1}·h^{-1}，间断追加罗库溴铵 0.1 mg/kg，维持 BIS 40~60。术中维持 HR、MAP 在基础值的±20%。术毕待患者苏醒后移除喉罩，转送入麻醉复苏室。

1.3　*观察指标*　记录患者一般情况、睫毛反射消失时间、镇静成功率、喉罩初次置入成功率、诱导期血管活性药物使用情况；记录患者入室后（T_0）、插管前（T_1）、插管后即刻（T_2）、插管后 3 min（T_3）的

MAP、HR 及 BIS 值；记录 T_1、T_3 的血糖及乳酸；记录诱导期注射痛（分别为无、轻微、中度及剧烈注射痛）、低血压（下降>30%基础值）、心动过缓（下降>20%基础值）、呃逆、苏醒期躁动等；记录出复苏室时患者满意度及有无术中知晓、头晕、恶心呕吐等不良反应。

1.4　*统计学方法*　使用 Stata 17.0 进行统计分析。近似正态分布的计量资料表示为 $\bar{x}\pm s$，组间比较采用 ANOVA 检验。偏态分布的计量资料表示为中位数（四分位距），比较采用 Kruskal-Wallis 非参数检验。计数资料以例（%）表示，比较采用 χ^2 检验，等级资料采用秩和检验。多因素分析采用二分类变量的多元 logistic 回归。重复测量数据采用线性混合模型比较，并以最大似然法估计组间差异。两两比较时计量资料采用 Bonferoni 法校正，计数资料采用 χ^2 分割法校正。以 P<0.05 为差异有统计学意义。

2　结　果

2.1　*一般情况*　本研究初始筛选患者 126 例，最终纳入患者 117 例，其中瑞马唑仑组 42 例，环泊酚组 36 例，丙泊酚组 39 例。剔除原因：抗生素过敏 1 例，手术暂停 2 例，数据收集不全 6 例。三组患者的一般资料比较差异无统计学意义（P>0.05）。见表 1。

2.2　*诱导期主要指标*　三组均诱导成功。三组诱导期主要观察指标的单因素比较见表 2。瑞马唑仑组诱导期低血压、低心率及使用血管活性药物发生率最低（P<0.05）。多因素分析显示，瑞马唑仑是诱导期低血压和低心率的独立性保护因素（P<0.01）。见表 3、表 4。

2.3　*诱导期其他指标*　三组 $T_{0\sim3}$ 时点的 BIS 值、HR 变化幅度、MAP 变化幅度，T_1 和 T_3 时点血乳酸和血糖水平的差值比较，见图 1。三组 BIS 值变化差异无统计学意义（P>0.05）。MAP 变化幅度（似然比 χ^2 = 14.080，P = 0.001）及 HR 变化幅度（似然比 χ^2 = 41.690，P<0.01）差异均有统计学意义。血乳酸和血糖差值差异无统计学意义（P>0.05）。

2.4　*不良反应*　诱导期注射痛瑞马唑仑组 6 例（14%），均为中度；环泊酚组 0 例；丙泊酚组 21 例（54%），轻、中度疼痛各 9 例，重度 3 例。三组注射痛发生率差异有统计学意义（χ^2 = 33.429，P<0.01）。丙泊酚组注射痛发生率分别显著高于瑞马唑仑组和环泊酚组，差异均有统计学意义（P<0.017），而瑞马唑仑组与环泊酚组注射痛发生率差异无统计学意义（P>0.017）。三组均无呃逆、术中知晓、苏醒期躁动、头晕或恶心呕吐发生。三组患者满意度均为 100%。

表 1　三组患者一般情况的比较

Tab. 1　Comparison of general conditions among three groups of patients

组别	例数	男/女（例）	年龄（岁，$\bar{x}\pm s$）	BMI（kg/m^2，$\bar{x}\pm s$）	ASA 分级（例，Ⅰ/Ⅱ/Ⅲ级）	手术时长[min，$M(IQR)$]
瑞马唑仑组	42	36/6	60.70±15.00	24.40±2.90	3/30/9	48(55)
环泊酚组	36	24/12	59.90±10.80	23.50±3.50	0/30/6	45(70)
丙泊酚组	39	27/12	60.50±12.60	24.00±2.90	6/27/6	40(15)
$\chi^2/F/Z$ 值		4.496	0.040	0.800	2.271	0.328
P 值		0.106	0.962	0.454	0.321	0.849

表 2　三组患者诱导期主要指标的比较　[例（%）]

Tab. 2　Comparison of main indicators during induction period among three groups of patients　[case（%）]

组别	例数	睫毛反射消失（s，$\bar{x}\pm s$）	喉罩初次成功	低血压	低心率	使用血管活性药物
瑞马唑仑组	42	49.90±14.90	33(79)	9(21)[a]	6(14)[a]	6(14)[a]
环泊酚组	36	50.80±16.40	33(92)	15(42)	18(50)	12(33)
丙泊酚组	39	45.70±12.00	36(92)	21(54)	12(31)	15(38)
F/χ^2 值		1.370	4.351	9.204	11.607	6.512
P 值		0.258	0.114	0.010	0.003	0.039

注：与丙泊酚组比较，[a]P<0.017。

表 3　诱导期低血压的相关危险因素的 logistic 回归分析

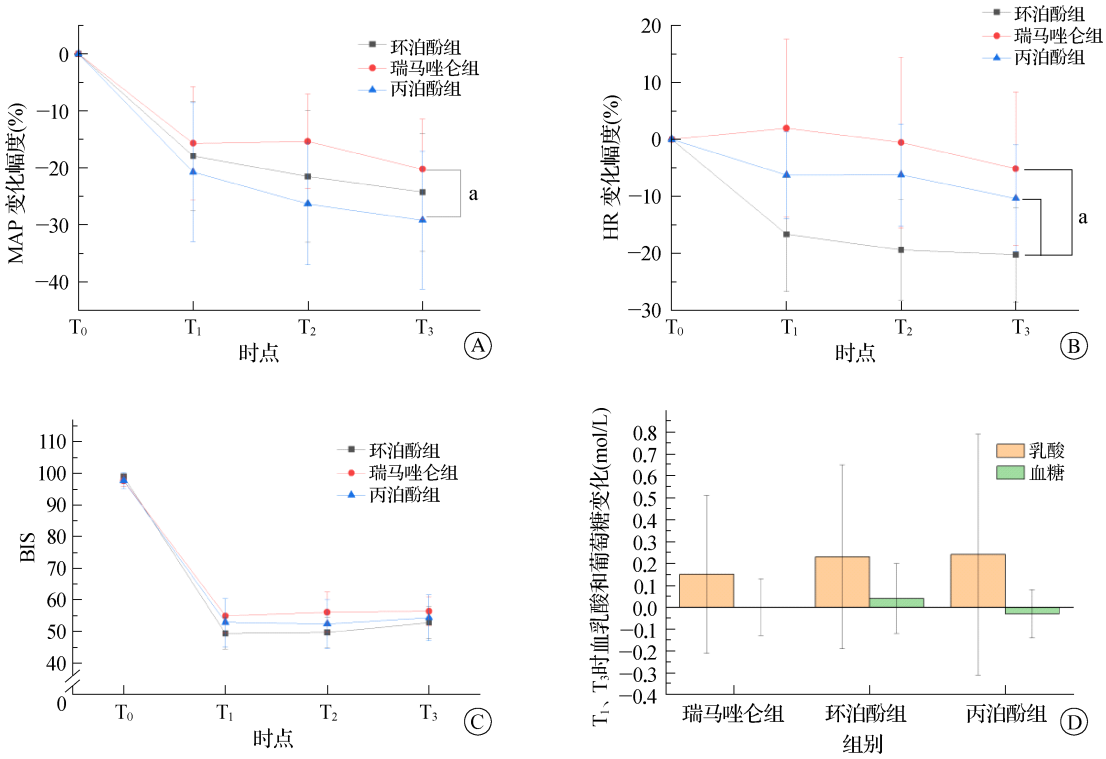
Tab. 3　Logistic regression analysis of risk factors associated with hypotension during induction

因素	β 值	*SE*	*OR*	*Wald* χ^2	*P* 值	95%*CI*
分组						
环泊酚	−0.496	0.479	0.609	1.070	0.301	0.238~1.559
瑞马唑仑	−1.612	0.516	0.199	9.744	0.002	0.073~0.549
丙泊酚	1					
性别						
男	1					
女	−0.792	0.499	0.440	0.453	0.113	0.170~1.206
ASA 分级						
Ⅰ+Ⅱ级	1					
Ⅲ级	−0.333	0.559	0.221	0.717	0.552	0.239~2.147
年龄	−0.016	0.016	0.990	0.984	0.324	0.953~1.016
BMI	0.010	0.068	1.044	1.010	0.882	0.885~1.153

表 4　诱导期低心率的相关危险因素的 logistic 回归分析

Tab. 4　Logistic regression analysis of risk factors associated with low heart rate during induction

因素	β 值	*SE*	*OR*	*Wald* χ^2	*P* 值	95%*CI*
分组						
环泊酚	1					
瑞马唑仑	−1.757	0.563	0.173	9.721	0.002	0.057~0.520
丙泊酚	−0.827	0.485	0.437	2.904	0.088	0.169~1.132
性别						
男	1					
女	0.371	0.483	1.449	0.591	0.442	0.562~3.735
ASA 分级						
Ⅰ+Ⅱ级	1					
Ⅲ级	−0.110	0.574	0.896	0.037	0.848	0.291~2.759
年龄	0.009	0.018	1.009	0.270	0.603	0.974~1.045
BMI	0.023	0.069	1.023	0.109	0.741	0.894~1.171



注:A 为 MAP 变化;B 为 HR 变化;C 为 BIS 变化;D 为血乳酸和血糖变化;a 为 $P<0.05$。

图 1　三组诱导期 BIS、HR 波动幅度、MAP 波动幅度、血乳酸和血糖变化值的比较

Fig. 1　Comparison of BIS, HR fluctuation amplitude, MAP fluctuation amplitude, blood lactate and blood glucose changes during induction periods among three groups

3　讨　论

麻醉诱导是临床麻醉的开始,此阶段患者从清醒觉醒到麻醉状态,机体各个系统都发生了剧烈变化。目前临床常用麻醉诱导药物有经典药丙泊酚、我国自主研发新药环泊酚及将瑞芬太尼和咪达唑仑优点集于一身的新药瑞马唑仑。

本研究中三种药物用于麻醉诱导均安全、有效、快速,无需追加补救药物。三种药物均可导致麻醉诱导后低血压的发生,丙泊酚低血压作用最显著,环泊酚次之,瑞马唑仑对血压影响最小。丙泊酚快速且显著的降压作用,与其抑制心肌及降低全身血管阻力的双重循环抑制机制有关[1]。环泊酚表现出与丙泊酚相似的降压效果[4],与以往研究不同[2,5-6],分析认为与本研究中环泊酚诱导剂量的选择(0.4 mg/kg)有关。Duan 等[7]发现 0.3 mg/kg 环泊酚用于麻醉诱导时,不良事件发生率最低。在健康受试者中关于环泊酚和丙泊酚对急性血流动力学的影响结果显示,麻醉诱导后 5 min 内,两者对 MAP 的影响无差异[4],本研究结果与其一致。瑞马唑仑的降压作用显著弱于丙泊酚,这得益于使用瑞马唑仑诱导能较好地维持全身血管阻力水平[3]。值得注意的是三组低血压发生率均在 T_3 时点最高,提示喉罩置入刺激较小[6],可适当调整药物诱导剂量或更改药物使用方法(如靶控输注丙泊酚),临床上也应注意防范麻醉诱导后至手术开始前这段时期的低血压发生,及时补充液体和追加血管活性药物。

三组药物均可导致麻醉诱导后低心率的发生,环泊酚降低心率的作用显著(出现早且幅度大)。心率降低导致心输出量下降,进而导致血压下降,因此,推测环泊酚诱导后的低血压与其降心率的作用有关。Hasegawa 等[8]研究发现丙泊酚和瑞马唑仑均可降低麻醉诱导过程中自主神经的活动,不同的是瑞马唑仑维持了交感和副交感活动的平衡性,而丙泊酚则将其调节为交感神经支配。本研究中,丙泊酚和瑞马唑仑低心率作用均弱于环泊酚,推测环泊酚对于自主神经的影响机制与丙泊酚和瑞马唑仑可能都不同,有待进一步研究。本研究还发现,丙泊酚低心率作用弱于其低血压作用,分析认为与丙泊酚诱导后交感神经支配占优有关。

Ko 等[9]研究发现瑞马唑仑诱导的麻醉深度比丙泊酚浅。Chen 等[6]发现环泊酚诱导的 BIS 值明显低

于丙泊酚。本研究中,三种药物各时点 BIS 值虽无统计学差异,但趋势与上述研究一致。分析认为:(1) 三种药物诱导的麻醉深度可能确实存在差异;(2) 瑞马唑仑的镇静水平与 BIS 值相关性不如其他两种药物[10-11]。此外,瑞马唑仑镇静峰值滞后于环泊酚和丙泊酚,血浆半衰期也长于两者[12],或许是导致瑞马唑仑组喉罩置入初次成功率略低于环泊酚组和丙泊酚组的原因,但瑞马唑仑组的低喉罩初次置入成功率也可能与瑞马唑仑对咽反射抑制轻有关[13]。

与环泊酚和丙泊酚相比,瑞马唑仑诱导后血糖波动更小,但差异无统计学意义。吴宣等[14]研究发现 0.2 mg/kg瑞马唑仑可抑制腹腔镜胆囊切除术患者全麻诱导期的应激反应。赵晓宇等[15]也发现瑞马唑仑(0.3 mg/kg)在宫腔镜手术患者全麻诱导中有抑制应激的作用。分析认为与苯二氮䓬类药物在应激时可抑制促肾上腺皮质激素和皮质醇浓度有关,也可能与瑞马唑仑在诱导期间维持了更稳定的 HR 和 MAP 有关[16]。此外,三种药物诱导对血乳酸的影响都很小。

综上所述,瑞马唑仑、环泊酚、丙泊酚均可成功用于麻醉诱导。瑞马唑仑血流动力学最平稳,丙泊酚降低血压作用最显著,环泊酚降低心率作用最明显。瑞马唑仑与环泊酚几乎无注射痛[5]。临床上应根据手术种类、麻醉方案、麻醉医生用药习惯及患者自身状况合理选择药物,并加强监测。

利益冲突　无

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