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Effects of different doses of remimazolam on hemodynamics during general anesthesia in patients with septic shock

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Abstract. – OBJECTIVE: The stability of hemodynamics plays a vital role in the process of anesthesia induction for patients with septic shock. As a new-type benzodiazepine, remimazolam has numerous advantages, including rapid induction, rapid recovery, stable hemodynamics, and mild respiratory depression. Nevertheless, reports about the effects of remimazolam on hemodynamics in patients with septic shock are still limited. The study aimed to evaluate the effects that different doses of remimazolam have on hemodynamics in inducing general anesthesia in patients with septic shock.

PATIENTS AND METHODS: Admitted to the intensive care unit of our hospital from January 2023 to June 2023, 75 patients with septic shock caused by acute appendicitis-induced sepsis were selected as observation subjects. They were randomly assigned to receive low-dose [0.2 mg/(kg·h)], medium-dose [0.3 mg/(kg·h)], and high-dose [0.4 mg/(kg·h)] remimazolam by using a random number table, with 25 patients in each group. Their intraoperative conditions were recorded, including operation duration, intraoperative hemorrhage volume, intraoperative transfusion volume, and decannulation time. Hemodynamic parameters, including mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), and stoke volume index (SVI) were collected at seven-time points (T0: before induction; T1: before intubation; T2: after intubation; T3: the start of operation; T4: 15 min after operation; T5: 30 min after operation; T6: the end of operation). We also compared hepatic and renal function indexes, including blood urea nitrogen (BUN), serum creatinine (sCr), procalcitonin (PCT), white blood cells (WBC), tumor necrosis factor-α2 (TNF-α2), and Interleukin-6 (IL-6), of the three groups of patients before operation and 1, 3, 5, 7 days after operation. In addition, the incidence of adverse reactions in the three groups was recorded and compared.

RESULTS: During remimazolam induction, the number of patients with intraoperative need for rescue remimazolam in the medium-dose and high-dose groups was significantly lower than in the low-dose group ($p < 0.05$). In terms of hemodynamic indexes, MAP in the high-dose group at T2 was lower than that at T0 ($p < 0.05$), and MAP at T2 was significantly lower in the high-dose group than that in the medium-dose group ($p < 0.05$). Furthermore, MAP at T4 in the medium-dose and high-dose groups declined compared with the low-dose group ($p < 0.05$). There were no significant differences in HR, CI, and SVI at different time points among the three groups ($p > 0.05$), but levels of HR and SVI decreased and CI increased after anesthesia compared with those before operation. Additionally, in comparison with the levels before operation, levels of sCR, BUN, PCT, WBC, TNF-α, and IL-6 were higher on postoperative days 1, 3 ($p < 0.05$) and lower on postoperative day 7 ($p < 0.05$). After the operation, both levels of BUN and sCR in the medium-dose and high-dose groups were lower than those in the low-dose group ($p < 0.05$).

CONCLUSIONS: Remimazolam is safe and effective for inducing general anesthesia in patients with septic shock. Low, medium, and high doses of remimazolam can maintain a stable hemodynamic state, and the recovery of hepatic and renal function is certain to depend on the dose.

Key Words:
Remimazolam, Anesthesia induction, Septic shock, Hemodynamics.

Introduction

Septic shock is a subset of sepsis. In the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[1], sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection, while septic shock is a medical condition with hypotension, shock, organ failure, and other manifestations. Patients with septic shock can be identified with a clinical construct of sepsis with persisting

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hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg and having a serum lactate (SI) level > 2 mmol despite adequate volume resuscitation[2]. Controlling infections is equally important to resuscitation in the treatment of septic shock. When invasive diagnosis or treatment is required, the preoperative management of anesthesia is closely related to the severity of the patient's disease[3]. Because of the instability of hemodynamics in septic patients, anesthesia induction may trigger vasodilation and myocardial depression, leading to serious hypotension and worsening hemodynamics[4].

Remimazolam is a new drug of ester-benzodiazepine derivative, synthesized by introducing a metabolizable side chain (methyl propionate) based on the structure of midazolam. It mainly works on γ-aminobutyric acid type A receptor (GABAAR) and is a benzodiazepine sedative-hypnotic drug with the characteristics of water-soluble and non-irritating[5]. It has advantages, including rapid induction, rapid recovery, stable hemodynamics, and mild respiratory depression. Additionally, remimazolam has a high clearance rate and metabolism independent of the liver and kidneys, and thus, it causes no accumulation after long-term infusion[6,7]. A recent clinical trial[8] reported that remimazolam combined with alfentanil can better preserve patient respiration and reduce the incidence of respiratory depression during painless fibreoptic bronchoscopy compared with isoproterenol. Rogers and McDowell[6] illustrated the mechanism of remimazolam to increase the frequency of chloride ion channel opening in neuronal cell membranes and membrane permeability by binding to GABAAR. Then chloride ions enter the cell along a concentration gradient, increasing internal membrane potential and consequently triggering hyperpolarization and decreased excitability. As a result, neuronal electrical activity can be inhibited to produce sedative effects, and the onset time of remimazolam is 1-3 min[6]. Remimazolam also has a quick offset because it is metabolized independently of cytochrome oxidase but is mainly degraded by non-specific esterases to an inactive metabolite CNS7054[9]. Furthermore, on account of the high clearance and short half-life after constant intravenous infusion (7-8 min), long-time and high-dose use of remimazolam does not easily cause drug accumulation[10,11]. Collectively, remimazolam has a bright application prospect in clinical anesthesia, but there is limited literature on its application in surgical anesthesia for patients with septic shock. Thus, the study aimed to evaluate the effects of induction of general anesthesia with remimazolam on hemodynamics in patients with septic shock.

Patients and Methods

Study Subjects

75 patients with septic shock caused by acute appendicitis-induced sepsis admitted to the intensive care unit (ICU) of Cangzhou Central Hospital from January 2023 to June 2023 were selected as observation subjects. The study analyzed the effects of induction of general anesthesia with different doses of remimazolam on hemodynamics in patients with septic shock. This study was approved by the Ethics Committee of Cangzhou Central Hospital (2022-059-01-z).

A random number table was adopted to divide the patients into low-dose group [n = 25, 0.2 mg/(kg·h)], medium-dose group [n = 25, 0.3 mg/(kg·h)] and high-dose group [n = 25, 0.4 mg/(kg·h)]. Inclusion criteria were as follows: (1) a diagnosis of sepsis-caused meeting the diagnostic criteria of the Chinese Guidelines for Management of Sepsis and Septic Shock (2018); (2) age between 16 and 85 years; (3) patients admitted to the ICU within 24 hours from the onset of the disease; (4) a clear diagnosis of acute appendicitis which required surgical treatment with general anesthesia. Exclusion criteria were as follows: (1) death within 24 hours of admission; (2) tumors of the heart, liver, kidney, and other organs; (3) acute coronary syndrome; (4) communication disorders; (5) incomplete medical records.

Data Collection

Basic information about the patients with septic shock was collected on the day of admission, including age, sex, education level, body mass index, underlying diseases, ICU stay, Acute Physiology and Chronic Health Evaluation (APACHEII) score, Sequential Organ Failure Assessment (SOFA) score, American Society of Anesthesiologists (ASA) classification, Glasgow Coma Scale (GCS) score, and Multiple Organ Dysfunction Score (MODS).

Anesthesia Methods

Three groups of patients were given low [0.2 mg/(kg·h)], medium (0.3 mg/kg·h) and high (0.4 mg/kg·h) doses of remimazolam (batch number: 32200718; strength: 36 mg; Jiangsu Hengrui

Pharmaceuticals Co., Ltd., Jiangsu, China) for anesthesia, respectively. All patients were routinely subjected to 6-8 hours of fasting and 2-4 hours of water deprivation. Peripheral venous access was established after the patients entered the operating room. Then, they were monitored for heart rate (HR), bispectral index (BIS), and electrocardiogram. The patients received invasive arterial catheterization, and MAP was monitored. All groups were given 3 minutes of preoxygenation (flow rate: 5 L/min) before anesthesia induction with remimazolam. Without a loading dose, remimazolam administration was completed within 30 seconds. When the BIS value was ≤ 60, the patients were continuously given cisatracurium 0.2 mg/kg (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Jiangsu, China) and intravenously injected with fentanyl 4 μ (Yichang Renfu Pharmaceuticals Co., Ltd., Hubei, China). When the BIS value was > 60, 0.05 mg/kg of remimazolam was intravenously injected once again until the BIS value ≤ 60, followed by tracheal intubation for surgery.

Index Observation

The following indexes were observed in the three groups of patients: 1) intraoperative conditions: operation duration, intraoperative hemorrhage volume, intraoperative transfusion volume, decannulation time, and the number of patients with intraoperative need for rescue remimazolam; 2) hemodynamic indexes: MAP, HR, cardiac index (CI) and, stoke volume index (SVI) at 7-time points before induction (T0), before intubation (T1), after intubation (T2), the start of operation (T3), 15 min after operation (T4), 30 min after operation (T5), and the end of operation (T6); 3) hepatic and renal function indexes: blood urea nitrogen (BUN), serum creatinine (sCr), procalcitonin (PCT), white blood cells (WBC), tumor necrosis factor-α2 (TNF-α2), and interleukin-6 (IL-6) at before operation and 1, 3, 5, 7 days after operation; 4) adverse reactions and prognosis: intraoperative hypoxemia, respiratory depression, emergence agitation, and postoperative nausea and vomiting, dizziness.

Statistical Analysis

Statistics analysis was conducted using the software SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data that conformed to a normal distribution were expressed as ($\bar{x} \pm s$) and a *t*-test was used for comparison between two groups, one-way analysis of variance (ANOVA) for comparison among multiple groups, and repeated measures ANOVA for comparison at different time points. Qualitative data were subjected to χ^2 test. $p < 0.05$ was considered significant.

Results

Baseline Characteristics of Patients

The low-dose group contained 18 males and 7 females, aged 37-98 years (average age: 69.64 ± 16.41 years) and an ICU stay of 8-19 hours (average ICU stay: 11.84 ± 2.59 hours). In the low-dose group, there were 15 cases of hypertension, 4 cases of diabetes, 10 cases of hyperlipidemia, and 2 cases of coronary heart disease. The medium-dose group consisted of 14 males and 11 females, with an age of 24-97 years (average age: 65.8 ± 17.66 years) and an ICU stay of 5-19 hours (average ICU stay: 1.16 ± 3.66 hours). In the medium-dose group, there were 13 cases of hypertension, 5 cases of diabetes, 10 cases of hyperlipidemia, and 4 cases of coronary heart disease. The high-dose group included 13 males and 12 females, aged 32-91 years (average age: 67.28 ± 15.58 years) and an ICU stay of 5-18 hours (average ICU stay: 11.84 ± 3.66 hours). In the high-dose group, there were 11 cases of hypertension, 3 cases of diabetes, 11 cases of hyperlipidemia, and 4 cases of coronary heart disease. The three groups showed no significant difference in the baseline characteristics ($p < 0.05$), indicating that the data of the three groups were comparable (Table I).

Intraoperative Conditions of the Three Groups of Patients

Operation duration, intraoperative hemorrhage volume, intraoperative transfusion volume, and decannulation time of the patients in the high, medium and low-dose groups were recorded and compared. The results illustrated that compared with the low-dose group, the number of patients with intraoperative need for rescue remimazolam was significantly lower in the other two groups ($p < 0.05$). Nevertheless, there was no significant difference in operation duration, intraoperative hemorrhage volume, intraoperative transfusion volume, and decannulation time among the three groups ($p < 0.05$) (Table II).

Table I. Baseline characteristics of patients with high, medium, and low doses of remimazolam.

	Low dose (n = 25)	Medium dose (n = 25)	High dose (n = 25)	F/H/χ^2	*p*
Age (year)	69.64 ± 16.41	65.8 ± 17.66	67.28 ± 15.58	0.341	0.712
Sex (%)				2.333	0.311
Male	18 (72.0)	14 (56.0)	13 (52.0)		
Female	7 (28.0)	11 (44.0)	12 (48.0)		
BMI (kg/m^2)	22.04 ± 2.47	22.57 ± 2.21	21.33 ± 2.2	1.818	0.170
Education level (%)				0.502	0.973
Primary school or below	15 (60.0)	16 (64.0)	17 (68.0)		
Junior or senior high school	7 (28.0)	7 (28.0)	6 (24.0)		
College or above	3 (12.0)	2 (8.0)	2 (8.0)		
Hypertension (%)				1.282	0.527
No	10 (40.0)	12 (48.0)	14 (56.0)		
Yes	15 (60.0)	13 (52.0)	11 (44.0)		
Diabetes (%)				0.601	0.741
No	21 (84.0)	20 (80.0)	22 (88.0)		
Yes	4 (16.0)	5 (20.0)	3 (12.0)		
Hyperlipidemia (%)				0.325	0.850
No	15 (60.0)	13 (52.0)	14 (56.0)		
Yes	10 (40.0)	12 (48.0)	11 (44.0)		
Coronary heart disease (%)				0.996	0.608
No	23 (92.0)	21 (84.0)	21 (84.0)		
Yes	2 (8.0)	4 (16.0)	4 (16.0)		
ASA classification (%)				0.987	0.611
I	5 (20.0)	8 (32.0)	6 (24.0)		
II	20 (80.0)	17 (68.0)	19 (76.0)		
ICU stay (d)	11.84 ± 2.59	11.16 ± 3.66	11.84 ± 3.66	0.345	0.709
APACHE II score	12.44 ± 3.22	13.04 ± 2.73	11.68 ± 2.43	1.471	0.237
SOFA score	9 (9,10)	9 (8,10)	9 (9,10)	2.061	0.357
GCS score	10.56 ± 1.69	10.64 ± 1.89	10.44 ± 1.66	0.083	0.921
MODS	8.72 ± 2.11	8.28 ± 2.30	8.36 ± 1.55	0.339	0.714

BMI: body mass index; ASA, American Society of Anesthesiologists; ICU, intensive care unit; APACHEII, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; GCS, glasgow coma scale; MODS, multiple organ dysfunction score.

Comparison of Hemodynamic Index Change at Different Time Points in the Three Groups

MAP, HR, CI, SVI at T0, T1, T2, T3, T4, T5 and T6 in the three groups were recorded. MAP level in the three groups decreased at T2 compared to T0. Particularly, the high-dose group showed a significant decline in MAP level at T2 compared with that at T0 and compared with that in the medium-dose group at T2 ($p < 0.05$). Compared with T0, MAP level at T4 showed a marked increase in the low-dose group ($p < 0.05$), but no

Table II. Comparison of intraoperative conditions among the three groups of patients.

Groups	n	Operation duration (min)	Intraoperative hemorrhage volume (ml)	Intraoperative transfusion volume (ml)	Decannulation time (min)	Intraoperative rescue remimazolam (%)
Low dose	25	214.08 ± 26.1	143.4 ± 11.34	92.4 ± 15.55	4 (4,5)	14 (56)
Medium dose	25	217.88 ± 25.91	146.6 ± 12.48	99 ± 13.15	5 (4,6)	3 (12)*
High dose	25	216.52 ± 30.88	147 ± 9.13	95.4 ± 16.07	5 (4,5)	4 (16)*
F/H/χ^2		0.121	0.794	1.217	3.050	14.683
p		0.887	0.456	0.302	0.218	0.001

*$p < 0.05$ *vs*. low-dose group.

significant changes in the medium-dose and high-dose groups; the latter two groups had a lower MAP level at T4 in comparison with the low-dose group ($p < 0.05$). Additionally, no significant differences were identified in HR, CI, and SVI at different time points or among the three groups ($p > 0.05$). Nevertheless, levels of HR and SVI after anesthesia were lower than that at T0, with the contrary trend of CI level (Table III). In general, intraoperative hemodynamic indexes for all patients were comparatively stable.

Comparison of Changes in Hepatic and Renal Function in the Three Groups of Patients

sCR, BUN, PCT, WBC, TNF-α, and IL-6 before the operation were collected and recorded. These indexes reached peaks at 1 day after operation and decreased to lower than the preoperative levels at 7 days after operation ($p < 0.05$). Specifically, at 1 and 3 days after the operation, sCR, BUN, PCT, WBC, TNF-α and IL-6 were significantly higher than that before the operation ($p < 0.05$), and both BUN and sCR of patients in the medium-dose and high-dose groups were lower than that in the low-dose group ($p < 0.05$). All these parameters decreased gradually from postoperative day 1 to day 5. On postoperative day 7, BUN in the medium-dose and high-dose groups and WBC in the high-dose group were markedly lower than those before the operation ($p < 0.05$). Meanwhile, both levels of BUN and sCR of patients in the medium-dose and high-dose groups were lower than those in the low-dose group after the operation ($p < 0.05$) (Table IV).

Incidence of Adverse Reactions in the Three Groups of Patients

The total incidence of adverse reactions during operation and after operation among three groups of patients was compared, including intraoperative hypoxemia, respiratory depression, emergency agitation, and postoperative nausea and vomiting, dizziness. In the low-dose group, there was 1 case of nausea and vomiting, 1 case of respiratory depression, 1 case of emergency agitation, and 1 case of dizziness. The medium-dose group had 4 cases of adverse reactions, including 1 case of nausea and vomiting, 2 cases of emergency agitation, and 1 case of dizziness. The high-dose group had six cases of adverse reactions, containing 2 cases of nausea and vomiting, 1 case of hypoxemia, 1 case of respiratory depression, and 2 cases of dizziness. There were no significant differences in the incidence of adverse reactions among the three groups ($\chi^2 = 0.682$, $p > 0.05$) (Table V).

Discussion

Based on BIS and Modified Observer's Assessment of Alertness/Sedation score, a previous clinical trial[12] of remimazolam confirmed that the depth and duration of sedation were closely dose-dependent. Schüttler et al[12] found healthy volunteers lost consciousness after 5 ± 1 minutes of intravenous injection of remimazolam, with 24 ± 6% decrease of MAP and 28 ± 15% increase of HR, no respiratory depression, and no prolongation of the QT interval. Additionally, they reported that single intravenous use of remimazolam (0.1-0.2 mg/kg) could quickly produce sedative effects, with a recovery time of 10-20 minutes and a high clearance. Pastis et al[13] reported the success rate of bronchoscopy with remimazolam sedation was 80.6%, and remimazolam registered shorter time to full alertness, fast neuropsychiatric recovery, and no respiratory depression. Therefore, remimazolam was considered safe and effective and was expected to replace midazolam as a preoperative anesthetic[13]. In a randomized, double-blind, controlled trial, the effect of remimazolam induction on the hemodynamics of patients undergoing valve replacement surgery was investigated; the results proved that remimazolam was safe and could be a promising alternative to propofol during anesthesia induction[14]. Thus, we aimed to further explore the safety and effects that different doses of remimazolam have on hemodynamics during the induction of general anesthesia in patients with septic shock.

To evaluate the safety of remimazolam induction, we compared different remimazolam dose groups in terms of operation duration, intraoperative hemorrhage volume, intraoperative transfusion volume, decannulation time, and the number of patients with intraoperative need for rescue remimazolam. The results showed that the number of patients with intraoperative remimazolam requirement in the high-dose and medium-dose groups was significantly fewer than in the low-dose group, while the other intraoperative indexes were not statistically significantly different. Therefore, these three doses of remimazolam can keep good intraoperative management for patients with septic

Table III. Comparison of hemodynamic index change at different time points among the three groups of patients.

	Groups	n	T0	T1	T2	T3	T4	T5	T6
MAP (mmHg)	Low dose	25	80.12 ± 5.74	77.92 ± 7.61	76.20 ± 8.58	77.68 ± 8.02	86.16 ± 8.46[a]	78.00 ± 8.19	79.44 ± 8.28
	Medium dose	25	78.36 ± 4.73	80.92 ± 6.18	78.04 ± 10.00	79.36 ± 9.46[a]	77.72 ± 8.51*	79.80 ± 6.63	79.16 ± 6.48
	High dose	25	79.24 ± 6.53	78.40 ± 7.73	71.48 ± 6.04[#a]	79.56 ± 8.25	79.84 ± 4.87*	78.96 ± 7.44	77.20 ± 7.61
	F		0.593	1.250	4.088	0.360	8.624	0.366	0.663
	p		0.555	0.293	0.021	0.699	0.000	0.695	0.518
HR (beat/min)	Low dose	25	100.40 ± 6.13	90.28 ± 6.19[a]	85.96 ± 5.32[a]	86.12 ± 6.22[a]	80.88 ± 6.45[a]	81.04 ± 5.63[a]	76.04 ± 6.41[a]
	Medium dose	25	98.80 ± 5.43	91.24 ± 5.67[a]	88.84 ± 8.07[a]	86.68 ± 6.71[a]	81.44 ± 6.74[a]	81.56 ± 6.70[a]	74.72 ± 5.99[a]
	High dose	25	98.64 ± 4.85	90.76 ± 6.98[a]	88.48 ± 5.08[a]	84.52 ± 4.40[a]	81.96 ± 6.33[a]	80.12 ± 6.10[a]	76.56 ± 5.35[a]
	F		0.784	0.145	1.548	0.914	0.172	0.350	0.639
	p		0.460	0.865	0.220	0.405	0.842	0.706	0.531
CI [L/ (min·m^2)]	Low dose	25	2.65 ± 0.34	3.05 ± 0.63[a]	3.81 ± 0.52[a]	4.09 ± 0.59[a]	4.17 ± 0.53[a]	4.12 ± 0.63[a]	4.11 ± 0.62[a]
	Medium dose	25	2.75 ± 0.47	3.32 ± 0.63[a]	3.64 ± 0.67[a]	4.16 ± 0.52[a]	4.20 ± 0.53[a]	4.36 ± 0.57[a]	4.08 ± 0.57[a]
	High dose	25	2.64 ± 0.70	3.25 ± 0.61[a]	3.56 ± 0.52[a]	4.22 ± 0.62[a]	4.21 ± 0.64[a]	4.34 ± 0.57[a]	4.07 ± 0.45[a]
	F		0.343	1.209	1.290	0.300	0.034	1.222	0.027
	p		0.711	0.304	0.282	0.742	0.967	0.301	0.974
SVI	Low dose	25	36.61 ± 1.64	34.07 ± 1.50[a]	31.58 ± 0.96[a]	29.81 ± 1.43[a]	30.41 ± 1.59[a]	29.98 ± 1.41[a]	29.47 ± 1.51[a]
	Medium dose	25	36.47 ± 2.34	33.85 ± 1.09[a]	31.94 ± 1.90[a]	29.71 ± 1.36[a]	30.03 ± 1.35[a]	29.58 ± 1.43[a]	30.00 ± 1.38[a]
	High dose	25	36.87 ± 1.30	33.61 ± 1.54[a]	31.09 ± 1.57[a]	29.40 ± 1.38[a]	30.15 ± 1.34[a]	29.60 ± 1.40[a]	29.69 ± 1.56[a]
	F		0.310	0.674	1.949	0.607	0.454	0.656	0.801
	p		0.735	0.513	0.150	0.548	0.637	0.522	0.453

[a]$p < 0.05$ *vs*. T0; [#]$p < 0.05$ vs. Medium dose; *$p < 0.05$ *vs*. Low dose. MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SVI, stoke volume index; T0, before induction; T1, before intubation; T2, after intubation; T3, the start of operation; T4, 15 min after operation; T5, 30 min after operation; T6, the end of operation.

Table IV. Comparison of changes in hepatic and renal function in the three groups of patients.

Groups	n	Before operation	1 day after operation	3 days after operation	5 days after operation	7 days after operation
BUN (mmol/L)						
Low dose	25	17.55 ± 1.76	31.84 ± 2.37[a]	23.02 ± 2.61[a]	18.41 ± 1.62[a]	13.38 ± 1.98[a]
Medium dose	25	17.39 ± 1.74	28.67 ± 1.81[a]*	21.18 ± 1.67[a]*	16.05 ± 1.53[a]*	12.02 ± 1.29a*
High dose	25	17.5 ± 1.50	27.65 ± 1.50[a]*	20.40 ± 2.45[a]*	15.14 ± 2.16[a]*	11.22 ± 2.13a*
F		0.056	32.171	8.691	22.243	8.818
p		0.945	< 0.001	< 0.001	< 0.001	< 0.001
sCR (mmol/L)						
Low dose	25	173.41 ± 27.07	284.23 ± 16.12[a]	240.19 ± 21.01[a]	196.28 ± 21.23[a]	161.81 ± 14.29[a]
Medium dose	25	174.05 ± 22.36	269.97 ± 29.09[a]*	224.00 ± 22.06[a]*	174.80 ± 19.58[a]*	149.19 ± 22.74a*
High dose	25	177.00 ± 21.63	266.75 ± 22.41[a]*	219.76 ± 24.35[a]*	165.19 ± 21.22*	146.09 ± 20.33a*
F		0.162	4.035	5.728	14.797	4.583
p		0.851	0.022	0.005	< 0.001	0.013
PCT (ng/ml)						
Low dose	25	4.02 ± 0.71	7.26 ± 0.63[a]	5.26 ± 0.74[a]	4.4 ± 0.88[a]	3.51 ± 0.51[a]
Medium dose	25	4.33 ± 0.69	7.20 ± 0.64[a]	5.53 ± 0.88[a]	4.31 ± 0.73[a]	3.48 ± 0.56[a]
High dose	25	4.20 ± 0.78	7.14 ± 0.75[a]	5.31 ± 0.73[a]	4.44 ± 0.84[a]	3.43 ± 0.40[a]
F		1.151	0.192	0.806	0.141	0.139
p		0.322	0.826	0.451	0.869	0.871
WBC (*109/L)						
Low dose	25	12.00 ± 0.92	21.94 ± 4.37[a]	16.76 ± 2.54[a]	13.59 ± 1.95[a]	8.64 ± 1.35[a]
Medium dose	25	11.60 ± 1.06	21.13 ± 3.14[a]	15.64 ± 2.52[a]	12.86 ± 1.19[a]	8.49 ± 0.95[a]
High dose	25	11.86 ± 1.05	21.12 ± 2.87[a]	16.95 ± 2.47[a]	13.36 ± 1.55[a]	8.12 ± 0.92[a]
F		0.993	0.446	1.987	1.387	1.517
p		0.375	0.642	0.145	0.256	0.226
TNF-α2 (ng/L)						
Low dose	25	34.77 ± 4.26	55.16 ± 2.87[a]	45.64 ± 3.88[a]	37.84 ± 3.40[a]	31.27 ± 3.23[a]
Medium dose	25	35.25 ± 4.92	55.56 ± 3.90[a]	44.69 ± 4.19[a]	37.10 ± 3.42[a]	31.60 ± 2.67[a]
High dose	25	35.16 ± 4.77	55.07 ± 3.90[a]	44.96 ± 4.40[a]	38.61 ± 2.79[a]	30.48 ± 3.29[a]
F		0.075	0.132	0.343	1.380	0.864
p		0.928	0.876	0.711	0.258	0.426
IL-6 (pg/ml)						
Low dose	25	29.74 ± 2.74	79.87 ± 2.56[a]	58.95 ± 2.38[a]	37.04 ± 2.14[a]	23.28 ± 3.00[a]
Medium dose	25	29.28 ± 2.41	79.07 ± 1.76[a]	58.72 ± 1.95[a]	37.27 ± 2.42[a]	23.90 ± 2.28[a]
High dose	25	29.97 ± 2.42	79.3 ± 2.19[a]	58.86 ± 2.56[a]	36.69 ± 1.95[a]	23.71 ± 2.62[a]
F		0.48	0.874	0.064	0.451	0.362
p		0.621	0.422	0.938	0.638	0.697

[a]$p < 0.05$ *vs*. before operation; *$p < 0.05$ *vs*. low dose. BUN, blood urea nitrogen; sCR, serum creatinine; PCT, procalcitonin; WBC, white blood cells; TNF-α2, tumor necrosis factor α2; IL-6, interleukin-6.

shock, and the high-dose remimazolam has a more pronounced sedative effect than low-dose and medium-dose remimazolam. Some adverse reactions were observed, but the incidence of adverse reactions was not statistically different among the three groups. Taken together, remimazolam is safe and effective for inducing intraoperative anesthesia in patients with septic shock.

Table V. Comparison of the incidence of adverse reactions among the three groups of patients.

Variables	Low dose	Medium dose	High dose	χ^2	*p*
n	25	25	25		
Nausea and vomiting (%)	1 (4.0)	1 (4.0)	2 (8.0)		
Hypoxemia (%)	0 (0.0)	0 (0.0)	1 (4.0)		
Respiratory depression (%)	1 (4.0)	0 (0.0)	1 (4.0)		
Emergence agitation (%)	1 (4.0)	2 (8.0)	0 (0.0)		
Dizziness (%)	1 (4.0)	1 (4.0)	2 (8.0)		
Total (%)	4 (16.0)	4 (16.0)	6 (24.0)	0.682	0.711

Early identification and diagnosis of septic shock are key to a good prognosis. The pathological mechanism of septic shock is mainly characterized by severe circulatory and cellular metabolic abnormalities[15]. Thus, hemodynamic monitoring, which contributes to restoring tissue hypoxia, repairing oxygen utilization of cells, and preventing organ failure, is fairly important for diagnosis, resuscitation, and hemodynamic therapy of patients with septic shock[16]. MAP is a reliable and vital index of tissue perfusion and recovery[17], and The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [1] recommends MAP $\geq$ 65 mmHg as a resuscitation target. Furthermore, regular indicators such as HR, blood pressure, CI, and SVI are important for evaluating and improving hemodynamics in patients with septic shock[18]. In this study, we observed the effects of three doses of remimazolam on hemodynamic parameters (MAP, HR, CI, SVI) at seven-time points (T0-T6). High-dose remimazolam decreased MAP more significantly than low-dose and medium-dose remimazolam, and MAP was still $\geq$ 65 mmHg. There were no marked differences in the other hemodynamic parameters among the three groups, but the levels of HR and SVI after anesthesia were lower than those before the operation, with the contrary trend of CI level. To sum up, hemodynamic parameters were stable in patients with septic shock after using remimazolam.

Critically ill patients (such as septic shock) may have parenchymal organ failure (such as liver and kidneys), and long-time use of sedatives easily produces drug accumulation[19]. In this study, the indexes of hepatic and renal function were observed. BUN and sCR increased in varying degrees on postoperative days 1, 3, and 5, but decreased back to near-normal levels on postoperative day 7. The increment in BUN and sCR in the medium-dose and high-dose groups were lower than that of the low-dose group, and the effect of high-dose remimazolam in regulating pathological increase of hepatic and renal function indexes was superior to that of medium and low doses. Therefore, our results indicate that remimazolam does not have a serious burden on the liver and kidneys in patients with septic shock, which is in line with the previous research in the literature on the pharmacological characteristics of remimazolam.

Some research reports[20,21] reported the regulation effect of propofol on inflammation. Liu et al[22] found that PCT had a higher prognostic value than C-reactive protein for 30-day all-cause mortality in patients with septic shock. In this study, the changes in PCT, WBC, TNF-α, and IL-6 before and after the operation were monitored. The levels of the inflammatory indicators in the three groups reached their peaks on day 1 after the operation and were significantly lower on postoperative day 7 than those before the operation. There were no significant differences in the changes of inflammatory indicators among the three groups, but high-dose remimazolam has an evident decreasing effect on WBC on postoperative day 7. The above results indicate that remimazolam has an inhibitory effect on inflammation in the body after the operation.

Collectively, the aforementioned findings showed that different doses of remimazolam could effectively maintain a stable hemodynamic state during general anesthesia in patients with septic shock, providing great management of preoperative anesthesia for later invasive surgical diagnosis and treatment. In addition, postoperative recovery of hepatic and renal function was dose-dependent with remimazolam. An ideal sedative for critically ill patients requiring preoperative anesthesia should have a rapid onset of effect and be metabolized without reliance on any specific organ system[23]. Remimazolam is degraded by non-specific esterase without dependence on cytochrome oxidase and dependence on the liver and kidneys. Given these advantages, remimazolam is considered to be an appropriate sedative for preoperative anesthesia in patients with septic shock. Our study expands the database of clinical use of remimazolam and provides important data on the use of anesthetic drugs in patients with septic shock who need invasive diagnosis and treatment. However, due to limitations of funds and time, the study still has space to be developed more completely and deeply. Additionally, there is no clear explanation of the dose-dependent contribution of remimazolam to the improvement of hepatic and renal function.

Conclusions

In this small-scale pilot research, it is safe and effective to use low [0.2 mg/(kg·h)], medium [0.3 mg/(kg·h)] and high [0.4 mg/(kg·h)] doses of remimazolam to induce general anesthesia in patients with septic shock. None of the three doses have any significant effects on the hemodynamics indexes of the patients, and postoperative recovery of hepatic and renal function is dose-dependent with remimazolam.

Informed Consent
All the included patients in this study signed the informed consent form.

Ethics Approval
This study was approved by the Ethics Committee of Cangzhou Central Hospital (2022-059-01-z).

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Authors' Contributions
Qing-chun Dai and Jing-lin Zhao designed the study and wrote the main manuscript text. Xiao-yun Miao, Rui Wang, and Zhi Hui collected, interpreted, and statistically analyzed the data for the study. The authors read and approved the final manuscript.

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Availability of Data and Materials
The dataset supporting the conclusions of this article is available at our institution, contacting the corresponding author.

Conflicts of Interest
This study has no conflict of interest.

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