

Prospective Study

Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia

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Abstract

BACKGROUND

Sedation with propofol injections is associated with a risk of addiction, but remimazolam benzenesulfonate is a comparable anesthetic with a short elimination half-life and independence from cell P450 enzyme metabolism. Compared to remimazolam, remimazolam benzenesulfonate has a faster effect, is more quickly metabolized, produces inactive metabolites and has weak drug interactions. Thus, remimazolam benzenesulfonate has good effectiveness and safety for diagnostic and operational sedation.

AIM

To investigate the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

METHODS

A total of 80 patients who underwent surgery in the Department of Cardiothoracic Surgery from August 2020 to April 2021 were included in the study. Using a random number table, patients were divided into two anesthesia induction groups of 40 patients each: remimazolam (0.3 mg/kg remimazolam benzenesulfonate) and propofol (1.5 mg/kg propofol). Hemodynamic parameters, inflammatory stress response indices, respiratory function indices, perioperative indices and adverse reactions in the two groups were monitored over time for comparison.

RESULTS

At pre-anesthesia induction, the remimazolam and propofol groups did not differ regarding heart rate, mean arterial pressure, cardiac index or volume per wave index. After endotracheal intubation and when the sternum was cut off, mean arterial pressure and volume per wave index were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$). After endotracheal

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intubation, the oxygenation index and the respiratory index did not differ between the groups. After endotracheal intubation and when the sternum was cut off, the oxygenation index values were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$). Serum interleukin-6 and tumor necrosis factor- α levels 12 h after surgery were significantly higher than before surgery in both groups ($P < 0.05$). The observation indices were re-examined 2 h after surgery, and the epinephrine, cortisol and blood glucose levels were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$). The recovery and extubation times were significantly lower in the remimazolam group than in the propofol group ($P < 0.05$); there were significantly fewer adverse reactions in the remimazolam group (10.00%) than in the propofol group (30.00%; $P < 0.05$).

CONCLUSION

Compared with propofol, remimazolam benzenesulfonate benefited cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations. Remimazolam benzenesulfonate influenced the surgical stress response and respiratory function, thereby reducing anesthesia-related adverse reactions.

Key Words: Anesthesia; Thoracic surgery; Cardiac surgery; Cardiopulmonary bypass; Hemodynamics; Propofol; Drug-related side effects; Adverse reactions

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Core Tip: Remimazolam benzenesulfonate anesthesia has good effectiveness and safety for diagnostic and operational sedation but has not been evaluated for cardiac surgery. This study investigated the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia. Compared with propofol, remimazolam benzenesulfonate benefitted cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations and influencing the surgical stress response and respiratory function, thereby reducing anesthesia-related adverse reactions.

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INTRODUCTION

Open heart surgery under cardiopulmonary bypass (CPB) is the most traumatic surgery conducted in the clinic[1]. When CPB begins, the catecholamine concentration decreases due to the change in the blood perfusion pattern and decrease in blood viscosity, increasing the breadth of anesthesia. Consequently, the patient's blood pressure decreases. As CPB time increases, the patient's stress response leads to increased catecholamine secretion and blood viscosity, thereby increasing blood pressure[2,3]. There are different levels of cardiac dysfunction and hemodynamic changes in patients undergoing cardiac surgery. Cardiovascular reserve function in these patients is damaged, making it difficult for them to withstand the effects of anesthetics on circulatory function. Meanwhile, endotracheal intubation during surgery causes a stress response, which is not conducive to effective anesthesia induction[4]. Therefore, to maintain a good depth of anesthesia, understanding how to avoid excessive excitation and sympathetic and parasympathetic nerve inhibition while maintaining hemodynamic stability is key. Thus, choosing suitable anesthesia methods and drugs is crucial. Remimazolam benzenesulfonate, a novel benzodiazepine, is an ultra-short-acting sedative and anesthetic drug that acts on the central γ -aminobutyric acid type A receptor to open channels and increase the influx of chloride ions to hyperpolarize nerve membranes and inhibit neuronal activity. Therefore, remimazolam benzenesulfonate is fast-acting and quickly metabolized,

making it safe and effective[5,6]. Our study explored the clinical application of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

MATERIALS AND METHODS

Baseline data

In total, 80 patients who underwent surgery in the Department of Cardiothoracic Surgery from August 2020 to April 2021 were included. Patients were divided into two anesthesia groups (remimazolam and propofol) of 40 patients each using a random number table. Patients were included if they were between 19 and 75 years of age, required heart valve replacement surgery by the same medical staff at our hospital, were classified as American Society of Anesthesiologists grades I-III, had a total surgery time of less than 7 h and had normal preoperative liver, kidney and circulation functions. Patients were excluded if they had coagulation dysfunction, hypertension, anemia, acute myocardial infarction, viral myocarditis, atrioventricular block, cerebrovascular disease or poor blood glucose control.

Before commencement, the study plan was approved by the Medical Ethics Committee of our hospital, and the patients and their families signed informed consent forms.

Anesthesia methods

The remimazolam group received 0.3 mg/kg of remimazolam benzenesulfonate (Yichang Renfu Pharmaceutical Group Co. Ltd., Yichang, Hubei, China) for anesthesia induction within 30 s. If the bispectral index value was ≤ 60 , then 0.2 mg/kg of cisatracurium (Jiangsu Hengrui Pharmaceutical Co. Ltd., Jiangsu Province, China) and 4 $\mu\text{g}/\text{kg}$ of fentanyl (Yichang Renfu Pharmaceutical Co. Ltd.) were intravenously injected. Endotracheal intubation was performed after meeting the condition.

The propofol group received 1.5 mg/kg of propofol (Xi'an Libang Pharmaceutical Co., Ltd., Xi'an, Shaanxi, China) for anesthesia induction within 30 s. If bispectral index value was ≤ 60 , then 0.2 mg/kg of cisatracurium and then 4 $\mu\text{g}/\text{kg}$ of fentanyl were intravenously injected. Endotracheal intubation was performed after meeting the condition.

Observation indices and detection methods

Heart rate (HR), mean arterial pressure (MAP), cardiac index, volume per wave index (SVI), respiratory index (RI), oxygenation index (OI), serum interleukin-6 (IL-6) level, tumor necrosis factor alpha (TNF- α), norepinephrine (NE) level, epinephrine (E) level, cortisol (COR) level and blood glucose (GLU) level were measured preoperatively and 12 h postoperatively. Perioperative indicators, such as operative time, operative blood loss, intraoperative urine volume, CPB turnaround time, ascending aorta occlusion time, recovery time, extubation time, fluid volume and fentanyl dosage, were also recorded. Adverse reaction incidences were also recorded at different times [pre-anesthesia induction, after endotracheal intubation (T1), when the sternum was cut off (T2) and when the machine was shut down] to compare the two groups.

Not all patients needed medication before surgery. During the operation, an HP multifunction monitor (Philips Medical Systems, Germany) continuously monitored the patient's hemodynamic parameters, and GLU values were measured by arterial blood gas analysis. At each time point, 4 mL of arterial blood was extracted and centrifuged in a centrifuge with an 18-cm radius at a rotation speed of 2500 r/min for 15 min. The serum was separated and then stored at $-20\text{ }^{\circ}\text{C}$. Serum testing was performed using a kit (Beijing North Institute of Biotechnology), following the manufacturer's instructions. NE and E plasma concentrations were determined by high-performance liquid chromatography. The RI and OI were calculated as follows: $\text{OI} = \text{PaO}_2/\text{FiO}_2$; $\text{RI} = \text{P}(\text{A-a})\text{O}_2/\text{PaO}_2$.

Statistical analyses

The estimated HR, MAP, cardiac index and SVI values were tested by normal distribution test, and all were in line with approximately normal distribution or normal distribution, represented by mean \pm SD; *t*-tests were performed for comparisons between the groups. Enumeration data are expressed as percentages, and the χ^2 test was performed for comparison. SPSS version 21.0 (BM Corp., Armonk, NY, United States) was used for data processing with a test level of $\alpha = 0.05$.

RESULTS

Comparison of baseline conditions

Age, body mass index, blood pressure, HR, GLU, gender and the American Society of Anesthesiologists grade did not differ between the remimazolam and propofol groups ($P > 0.05$; [Table 1](#)).

Comparison of hemodynamic parameter

At pre-anesthesia induction, HR, MAP, cardiac index and SVI did not differ between the remimazolam and propofol groups ($P > 0.05$). At T1 and T2, MAP and SVI were significantly higher in the remimazolam group than in the propofol group ($P < 0.05$; [Table 2](#)).

Comparison of OI and RI

At T1, OI and RI did not differ between the remimazolam and propofol groups ($P > 0.05$). At T1 and T2, OI was significantly higher in the remimazolam group than in the propofol group ($P < 0.05$; [Table 3](#)).

Comparison of inflammatory serum markers

Serum IL-6 and TNF- α did not differ preoperatively or 2 h postoperatively between the remimazolam and propofol groups ($P > 0.05$). However, serum IL-6 and TNF- α were significantly higher in two groups 12 h after surgery compared to those before surgery ($P < 0.05$). Before surgery, NE, E, COR and GLU levels did not differ between the remimazolam and propofol groups ($P > 0.05$); however, 2 h after surgery, the E, COR and GLU levels were significantly higher in the remimazolam group than in propofol group ($P < 0.05$; [Table 4](#)).

Comparison of perioperative indicators

The operative time, operative blood loss, intraoperative urine volume, CPB transit time, ascending aorta occlusion time, fluid volume and fentanyl dosage did not differ between the two groups ($P > 0.05$). The recovery time and extubation time were significantly lower in the remimazolam group than in the propofol group ($P < 0.05$; [Table 5](#)).

Comparison of adverse reactions

There were significantly fewer adverse reactions in the remimazolam group (10.00%) than in the propofol group (30.00%) ($P < 0.05$; [Table 6](#)).

DISCUSSION

A series of experiments in China and abroad have demonstrated that using anesthetics, such as propofol, during the perioperative period can maintain hemodynamic stability by reducing the release of catecholamines and inflammatory factors[7-10]. In our study, at T1 and T2, MAP and SVI were higher in the remimazolam group than in the propofol group ($P < 0.05$), indicating that remimazolam benzenesulfonate had little effect on intraoperative hemodynamics. This may be because remimazolam benzenesulfonate can act on adrenergic receptors, inhibit NE release, reduce the catecholamine level as well as sympathetic nerve excitability, accelerate atrioventricular conduction and enhance myocardial contractility.

OI is a convenient measurement because it correlates well with hypoxia in the body and reflects the blood flow to the lungs. As such, it is currently the most commonly used index for monitoring lung oxygenation[11]. During cardiac surgery, the lung is often damaged, and the lung injury mechanism from cardiopulmonary bypass is complex[12]. In our study, at T2 (when the sternum was cut off) and when the machine was shut down, the OI in the remimazolam group was significantly higher than in the propofol group ($P < 0.05$), consistent with the literature[13,14]. This suggests that the intraoperative lung ventilation strategy and remimazolam benzenesulfonate use improve one-lung ventilation oxygenation and lung function, reduce pulmonary complications and have a protective effect on the lungs.

TNF- α is a substance that appears early in lung inflammation and has an important role in the pathological process of lung injury by stimulating the release of inflammatory mediators, such as IL-6 and IL-8[15]. IL-6 is involved in early inflammatory

Table 1 Comparison of the baseline conditions between the two groups

Baseline	Remimazolam group (n = 40)	Propofol group (n = 40)	t/ χ^2 value	P value
Age (yr)	54.9 ± 8.5	52.7 ± 7.0	1.264	0.210
BMI (kg/m ²)	24.1 ± 2.4	23.9 ± 2.2	0.389	0.699
Systolic blood pressure (mmHg)	126.3 ± 6.3	124.8 ± 8.1	0.925	0.358
Diastolic blood pressure (mmHg)	75.7 ± 6.0	76.5 ± 7.3	-0.535	0.594
Heart rate (times/min)	76.7 ± 7.1	78.2 ± 7.7	-0.906	0.368
Blood glucose (mmol/L)	5.39 ± 0.51	5.50 ± 0.48	-0.993	0.324
Gender, n (%)			1.270	0.260
Male	25 (62.50)	20 (50.00)		
Female	15 (37.50)	20 (50.00)		
ASA grades, n (%)			1.868	0.393
Grade I	8 (20.00)	6 (15.00)		
Grade II	20 (50.00)	26 (65.00)		
Grade III	12 (30.00)	8 (20.00)		

ASA: American Society of Anesthesiologists; BMI: Body mass index.

response and tissue damage; its expression level is related to the severity and duration of the inflammatory response[16]. Thus, it is an important indicator of the body's overall inflammatory and stress responses. In this study, we demonstrated that remimazolam benzenesulfonate anesthesia induction effectively reduced systemic inflammatory and oxidative stress responses in patients undergoing thoracoscopic cardiac surgery. The possible mechanisms are activated α o adrenergic receptors and inhibited nuclear factor kappa-B. Additionally, remimazolam benzenesulfonate maintained hemodynamic stability, only reducing the release of inflammatory mediators to a certain extent. In this study, the recovery time and extubation time of patients in the remimazolam group were significantly lower than in the propofol group, indicating that remimazolam benzenesulfonate maintained circulation as well as oxygen supply and demand balance. Remimazolam benzenesulfonate had a more stable and better effect on systemic circulation.

When a stress response occurs, the catecholamines secreted by the hypothalamic-pituitary-adrenal axis are excited to stimulate the locus coeruleus-sympathetic nerve-adrenal medulla system to produce E, NE and other hormones, which are used as indicators of the sensitivity and specificity of the stress response[17,18]. In this study, 2 h after surgery, the increase of E and COR were significantly lower in the remimazolam group than in the propofol group. This indicated that the increase of plasma E and COR concentrations could be inhibited and the stress response of patients could be reduced. Possible reasons for the elevated index were related to the continuous pumping of adrenaline after surgery and tracheal tube stimulation as the patient gradually woke up. There was an increasing trend in the NE concentration in both groups, though it was statistically insignificant and the specific reasons need to be further studied.

GLU is the main source of various tissues and cells in the body. A high GLU concentration during the perioperative period reduces the mitochondrial function in cells, destroys cell structures, affects inflammatory cell movement to the affected area, increases the infection surgical incision rate and affects wound healing[19]. When the body is in a stress response state, a large number of stress hormones, cytokines and inflammatory mediators are produced and released, making the tissue less sensitive to insulin, and thus, less insulin is secreted. As a result, glycogen decomposition and gluconeogenesis are enhanced. This results in a weakened ability to absorb and utilize GLU, which leads to an increase in GLU[20]. In this study, 2 h after surgery, the increase in GLU was significantly lower in the remimazolam group than in the propofol group ($P < 0.05$), verifying that intraoperative anesthesia induced by remimazolam benzenesulfonate maintained GLU stability during the perioperative period. Adverse reaction incidences were also significantly fewer in the remimazolam group than in the propofol group, suggesting that remimazolam benzenesulfonate is

Table 2 Comparison of the hemodynamic parameter between the two groups (mean ± SD)

Indicators	T0	T1	T2	T3
HR (times/min)				
Remimazolam group (<i>n</i> = 40)	76.7 ± 7.1	68.3 ± 6.5	66.8 ± 5.9	78.8 ± 6.6
Propofol group (<i>n</i> = 40)	78.2 ± 7.7	66.7 ± 6.7	65.1 ± 6.0	80.5 ± 7.3
<i>t</i> value	-0.906	1.091	1.278	-1.093
<i>P</i> value	0.368	0.279	0.205	0.278
MAP (mmHg)				
Remimazolam group (<i>n</i> = 40)	98.4 ± 5.3	88.3 ± 4.7	86.7 ± 4.2	102.1 ± 4.8
Propofol group (<i>n</i> = 40)	99.6 ± 4.7	86.0 ± 4.4	83.8 ± 4.5	103.8 ± 4.2
<i>t</i> value	-1.071	2.259	2.980	-1.686
<i>P</i> value	0.287	0.027	0.004	0.096
CI (L/min m ²)				
Remimazolam group (<i>n</i> = 40)	3.67 ± 0.62	3.52 ± 0.52	3.58 ± 0.48	3.57 ± 0.53
Propofol group (<i>n</i> = 40)	3.80 ± 0.60	3.40 ± 0.48	3.51 ± 0.50	3.65 ± 0.49
<i>t</i> value	-0.953	1.072	0.639	-0.701
<i>P</i> value	0.344	0.287	0.525	0.485
SVI (mL/m ² bpm)				
Remimazolam group (<i>n</i> = 40)	47.83 ± 5.81	43.80 ± 5.26	41.94 ± 5.57	45.80 ± 5.16
Propofol group (<i>n</i> = 40)	49.20 ± 5.63	40.38 ± 4.95	38.53 ± 4.86	43.73 ± 5.57
<i>t</i> value	-1.071	2.995	2.918	1.724
<i>P</i> value	0.287	0.004	0.005	0.089

CI: Cardiac index; HR: Heart rate; MAP: Mean arterial pressure; SVI: Volume per wave index; T0: Pre-anesthesia induction; T1: After endotracheal intubation; T2: When the sternum was cut off; T3: When the machine was shut down.

Table 3 Comparison of oxygenation index and respiratory index between the two groups (mean ± SD)

Indicators	T1	T2	T3
OI (mmHg)			
Remimazolam group (<i>n</i> = 40)	398.6 ± 24.7	357.6 ± 28.0	381.8 ± 30.0
Propofol group (<i>n</i> = 40)	390.1 ± 26.3	338.1 ± 30.5	359.4 ± 33.8
<i>t</i> value	1.490	2.979	3.135
<i>P</i> value	0.140	0.004	0.002
RI			
Remimazolam group (<i>n</i> = 40)	0.59 ± 0.17	0.90 ± 0.23	0.50 ± 0.18
Propofol group (<i>n</i> = 40)	0.62 ± 0.17	0.94 ± 0.21	0.56 ± 0.20
<i>t</i> value	-0.789	-0.812	-1.410
<i>P</i> value	0.432	0.419	0.162

OI: Oxygenation index; RI: Respiratory index; T1: After endotracheal intubation; T2: When the sternum was cut off; T3: When the machine was shut down.

safe and can make patients feel at ease, resulting in active cooperation with medical staff during treatment.

Currently, remimazolam benzenesulfonate has not been clinically used to induce anesthesia in cardiac surgery. However, remimazolam benzenesulfonate has a good anesthesia effect and is commonly used for clinical treatments and diagnostic

Table 4 Comparison of the serum levels of inflammatory factors between the two groups (mean \pm SD)

Groups	Remimazolam group (n = 40)	Propofol group (n = 40)	t value	P value
TNF- α (pg/mL)				
Before surgery	1.63 \pm 0.46	1.80 \pm 0.50	-1.583	0.118
12 h after surgery	3.74 \pm 0.95	3.98 \pm 1.03	-1.083	0.282
IL-6 (pg/mL)				
Before surgery	54.83 \pm 12.30	50.11 \pm 10.86	1.819	0.073
12 h after surgery	87.55 \pm 15.40	93.28 \pm 14.81	-1.696	0.094
E (pg/ μ L)				
Before surgery	1.58 \pm 0.38	1.49 \pm 0.40	1.032	0.305
12 h after surgery	2.52 \pm 0.70	2.86 \pm 0.76	-2.081	0.041
NE (pg/ μ L)				
Before surgery	2.66 \pm 0.48	2.48 \pm 0.51	1.625	0.108
12 h after surgery	3.38 \pm 0.75	3.73 \pm 0.88	-1.914	0.059
COR (ng/mL)				
Before surgery	22.73 \pm 4.81	21.40 \pm 4.36	1.296	0.199
12 h after surgery	34.20 \pm 6.85	31.06 \pm 5.72	2.225	0.029
GLU (mmol/L)				
Before surgery	5.39 \pm 0.51	5.50 \pm 0.48	-0.993	0.324
12 h after surgery	6.18 \pm 0.62	6.54 \pm 0.75	-2.34	0.022

COR: Cortisol; E: Epinephrine; GLU: Glucose; IL-6: Interleukin-6; NE: Norepinephrine; TNF- α : Tumor necrosis factor alpha.

Table 5 Comparison of the perioperative indicators between the two groups (mean \pm SD)

Indicators	Remimazolam group (n = 40)	Propofol group (n = 40)	t value	P value
Operative time (min)	249.6 \pm 18.5	245.8 \pm 17.0	0.957	0.342
Operative blood loss (mL)	308.4 \pm 20.7	304.1 \pm 18.6	0.977	0.331
Intraoperative urine volume (mL)	488.3 \pm 81.0	502.7 \pm 86.5	-0.769	0.444
CPB transit time (min)	115.8 \pm 9.8	113.5 \pm 10.6	1.008	0.317
Ascending aorta occlusion time (min)	76.4 \pm 5.1	78.1 \pm 6.3	-1.326	0.189
Recovery time (min)	121.1 \pm 18.0	140.2 \pm 21.5	-4.308	0.000
Extubation time (min)	158.3 \pm 24.7	174.9 \pm 28.6	-2.778	0.007
Fluid volume (mL)	1985.6 \pm 223.1	2056.7 \pm 245.7	-1.355	0.179
Fentanyl dosage (mg)	122.8 \pm 21.6	126.4 \pm 34.2	-0.563	0.575

CPB: Cardiopulmonary bypass.

operations. This study explored the anesthetic effect and safety of remimazolam benzenesulfonate-induced anesthesia by comparing it with propofol in patients who underwent cardiac surgery under general anesthesia to provide more information for creating clinical anesthesia plans.

CONCLUSION

Compared with propofol, anesthetic induction with remimazolam benzenesulfonate in

Table 6 Comparison of the adverse reactions between the two groups, *n* (%)

Groups	<i>n</i>	Nausea	Emesis	Hypotension	Drowsiness	Uroschesis	Incidence of adverse reactions
Remimazolam group	40	1	0	1	1	1	4 (10.00)
Propofol group	40	3	1	3	3	2	12 (30.00)
χ^2 value							5.000
<i>P</i> value							0.025

cardiac surgery patients under general anesthesia was better at reducing hemodynamic fluctuations caused by surgery, surgical stress response and anesthetic influence on respiratory function, thereby reducing anesthetic-related adverse reactions.

ARTICLE HIGHLIGHTS

Research background

Compared to remimazolam, remimazolam benzenesulfonate has a faster effect, is more quickly metabolized, produces inactive metabolites and has weak drug interactions. Remimazolam benzenesulfonate has good effectiveness and safety for diagnostic and operational sedation.

Research motivation

This study investigated the clinical value of remimazolam benzenesulfonate in cardiac surgery patients under general anesthesia.

Research objectives

In order to explore the clinical value of remimazolam benzenesulfonate under general anesthesia in patients undergoing cardiac surgery.

Research methods

In total, 80 patients who underwent surgery were included in the study. Using a random number table, patients were divided into two anesthesia induction groups of 40 patients each: Remimazolam and propofol. Hemodynamic parameters, inflammatory stress response indices, respiratory function indices, perioperative indices and adverse reactions in the two groups were monitored over time for comparison.

Research results

At pre-anesthesia induction, the remimazolam and propofol groups did not differ regarding heart rate, mean arterial pressure, cardiac index or volume per wave index. After endotracheal intubation and when the sternum was cut off, mean arterial pressure and volume per wave index were significantly higher in the remimazolam group than in the propofol group. After endotracheal intubation, the oxygenation index and the respiratory index did not differ between the groups. After endotracheal intubation and when the sternum was cut off, the oxygenation index values were significantly higher in the remimazolam group than in the propofol group. Serum interleukin-6 and tumor necrosis factor- α levels 12 h after surgery were significantly higher than before surgery in both groups.

Research conclusions

The results suggest that compared with propofol, remimazolam benzenesulfonate benefited cardiac surgery patients under general anesthesia by reducing hemodynamic fluctuations.

Research perspectives

Remimazolam benzenesulfonate can affect surgical stress response and respiratory function, thereby reducing adverse reactions related to anesthesia and has greater clinical promotion value.

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