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Original Research Article

Effect of general anesthesia with different doses of remimazolam on the depth of sedation and respiratory function in patients

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Abstract

Purpose: *To investigate the effect of general anesthesia using different doses of remimazolam on the depth of sedation and respiratory function in patients.*

Methods: *From August 2019 to May 2021, 120 patients admitted to Handan Central Hospital for general anesthesia were randomly assigned to propofol group (positive control) given the drug at a dose of 1.5 mg/kg, and three groups were given remimazolam (R) at a dose of 0.2 mg/kg (R1), 0.3 mg/kg (R2), or 0.4 mg/kg (R3) via intravenous injection. relation between Modified Observer Alertness/Sedation Scale (MOAA/S) scores and BIS was determined and recorded for the three remimazolam groups of patients. Systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation (SpO_2) levels were recorded. The Bruggrmann Comfort Scale (BCS) scale [8] was used at 4 score grades to assess the comfort level of the patients.*

Results: *The Modified Observer Alertness/Sedation Scale (MOAA/S) scores were positively correlated with Bispectral index (BIS); the higher the anesthesia dose, the higher the MOAA/S scores and BIS values of the patients. Patients in groups R1, R2, and R3 had significantly higher systolic blood pressure, diastolic blood pressure, heart rate, and oxygen saturation (SpO_2) at T2 than those in the propofol group ($p < 0.05$). Groups R1 and R2 exhibited considerably greater PAW values at T3 than the propofol group, whereas R3 had significantly lower PAW values at T3. There was significantly more incidence of bradycardia and hypotension in the propofol group than in the other three groups ($p < 0.05$).*

Conclusion: *General anesthesia with remimazolam at a dose of 0.3 mg/kg has no effect on respiratory function and hemodynamics, but it produces positive sedation and a high safety profile. However, more clinical trials are necessary prior to its application in clinical practice.*

Keywords: *Remimazolam, General anesthesia, Depth of sedation, Respiratory function, oxygen saturation (SpO_2)*

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INTRODUCTION

Surgery is an important clinical treatment modality in which the selection and use of anesthetic drugs are of particular significance [1]. However, anesthetics are associated with some adverse effects which may compromise postoperative recovery.

Patients are predisposed to dramatic hemodynamic fluctuations during anesthesia induction due to progressive decline in cardiovascular regulation and traumatic stress as well as the presence of multiple cardiovascular and cerebrovascular system disorders which increase the risk of adverse events such as cardiovascular and anesthetic risks [2].

Currently, propofol, etomidate and midazolam are widely used in clinical practice for the induction of intravenous anesthesia. Propofol is characterized by rapid onset of action, rapid recovery, short duration of action, and little irritation to the respiratory tract, but it suppresses the circulatory respiratory system. Etomidate is favored due to short duration of action and rapid onset, with less disturbance to the patient's hemodynamics and respiratory and circulatory systems. However, it inhibits adrenal cortical function. Midazolam is a commonly used anesthetic sedative for tracheal intubation, but patients are predisposed to respiratory depression, drowsiness, and lethargy, which are life-threatening conditions that require aggressive management with benzodiazepines [3].

Remimazolam is a newly-launched anesthetic drug. It is a water-soluble ultra-short-acting benzodiazepine drug which integrate the anesthetic safety of midazolam and the anesthetic effectiveness of propofol with a fast metabolism and a good safety profile. Pharmacological studies found that remimazolam acts mainly on the inhibitory neurotransmitter GABA receptors in the brain, enhances the activity of GABA receptors containing γ-subunits, and excites central nervous system by opening chloride channels and increasing chloride influx. Moreover, it increases cell membrane potential, hyperpolarizes the nerve cell membrane, inhibits neuronal activity, and relieves neuronal excitability, thereby reducing body activity, and causing sedation and amnesia [4]. Nonetheless, there is a dearth of systematic research on the use of remimazolam at appropriate doses for general anesthesia [5]. As a result, this study was carried out to investigate the effect of induction of general anesthesia with different doses of remimazolam on the depth of sedation and respiratory function of clinical patients, in order to establish a more solid foundation for its clinical application.

METHODS

Participants

One hundred and twenty patients who received general anesthesia for Surgery in Handan Central Hospital from august 2019 to May 2021 were recruited and randomly assigned to propofol group (positive control) given the drug at a dose of 1.5 mg/kg, and three remimazolam groups given remimazolam at a dose of 0.2 mg/kg (R1), 0.3 mg/kg (R2), or 0.4 mg/kg (R3) via intravenous injection. There were 30 patients in each group. Before enrolment, the study obtained signed informed consent from the patients. This study protocol was approved by the hospital ethics committee (approval no. GH-JU20190408). All procedures complied with the ethical guidelines of the declaration of Helsinki [6].

The randomization was carried out using an online web-based randomization tool (freely available at http://www.randomizer.org/). For concealment of allocation, the randomization procedure and assignment were managed by an independent research assistant who was not involved in screening or evaluation of the participants.

In the calculation of the original sample size, it was estimated that 100 patients in each group would be needed to determine a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

Inclusion and exclusion criteria

Inclusion criteria

Patients in the following categories were included in the study: patients who had complete medical data and did not revoke their consent, those who met the indications for tracheal intubation, with American Society of Anesthesiologists (ASA) Physical Status Classification of I-II [7]. Patients and their families understood the purpose and steps of this study and signed the informed consent form.

Exclusion criteria

Patients in the following categories were excluded: those with a history of drug allergy, patients with nasal bone deformity or history of trauma that prevented nasotracheal intubation, patients with coagulation abnormalities,

systemic diseases, anatomical abnormalities of the pharynx, or history of bronchial diseases, as shown by examination before the study; those who had psychiatric disorders or who were unable to complete the study successfully, and patients with atrioventricular block, sinus bradycardia, intracranial hypertension, craniocerebral injury and other diseases. Other excluded patients were those who had malignant tumors, patients who had long-term use of sedative and analgesic drugs, those with a history of opioid dependence or tolerance, and patients with allergic diseases.

Treatments and procedures

In the operating room, peripheral venous access of the patients was established for infusion of Ringer's lactate solution (Nanjing Xinfan Biotechnology Co. Ltd). The patients' vital signs and hemodynamics were closely monitored, and denitrogenated oxygen was administered for 3 min at a flow rate of 5 L/min before induction of anesthesia.

Propofol (Guangdong Jia Bo Pharmaceutical Co. Ltd; State Drug Administration H20051842; Specification: 200 mg/20 mL) was injected intravenously at a dose of 1.5 mg/kg within 30 s, and when the Bispectral index (BIS) value was ≤ 60, cisatracurium (Hangzhou Aoya Biotechnology Co. Ltd; State Drug Registration H20213438; specification: 5 mL/10 mg) and fentanyl (Jiangsu Enhua Pharmaceutical Co. Ltd; State Drug Registration H20113509; specification: 10 mL/0.5 mg) were injected intravenously at doses of 0.2 and 4 μg/kg, respectively, followed by tracheal intubation.

In groups R1, R2, and R3, remimazolam (Yichang Renfu Pharmaceutical Co. Ltd; State Drug Administration H20200006; specification: 25 mg) was given intravenously at doses of 0.2, 0.3 and 0.4 mg/kg, respectively, via intravenous injection within 30 sec. When BIS value was ≤ 60, intravenous injection of cisatracurium (Hangzhou Aoya Biotechnology Co. Ltd; State Drug Registration H20213438; specification: 5 mL/10 mg) and fentanyl (Jiangsu Enhua Pharmaceutical Co. Ltd; State Drug Registration H20113509; specification 0.5 mg/10 mL) were administered at doses of 0.2 and 4 μg/kg, respectively, followed by tracheal intubation. Tansnasal tracheal intubation was performed using a light-guided fiber-optic bronchoscope, and a ventilator was connected to establish a breathing circuit. The partial pressure of end-expiratory carbon dioxide (PET_{CO2}) was closely monitored in patients. Five minutes (5 min) after successful intubation, rocuronium bromide (Hainan Starr Pharmaceutical Co. Ltd; State Drug quantification H20203679; specification: 2.5 mL: 25 mg) and propofol (Xi'an Libang Pharmaceutical Co. Ltd; State Drug quantification H19990282; specification: 20 mL: 200 mg) were administered intravenously at doses of 1 and 1.5 mg/kg, respectively, prior to mechanical ventilation.

Evaluation of parameters/indicators

Correlation between Modified Observer Alertness/Sedation Scale (MOAA/S) scores and BIS was determined and recorded for the three remimazolam groups of patients.

Systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation (SpO_2) levels were recorded in the four groups of patients at T1 (before induction of anesthesia), T2 (after induction), and T3 (after intubation). Positive airway pressure (PAW) and end-tidal carbon dioxide partial pressure (PET_{CO2}) levels were recorded at T1 (before intubation), T2 (after intubation), and T3 (after extubation) in the four groups of patients.

The Bruggrmann Comfort Scale (BCS) scale [8] was used at 4 score grades to assess the comfort level of the four groups of patients, with 0 for constant pain, 1 for no pain when breathing normally, but severe pain on deep breathing or coughing; 2 for slight pain on deep breathing or coughing but no pain when lying still, 3 for no pain during deep breathing, and 4 for no pain during coughing.

The postoperative clinical sedation status of the four groups was evaluated with reference to the Ramsay Sedation Rating Scale, which has a total score of 6, with higher scores indicating better sedation [9]. The incidence of adverse reactions in the four groups was recorded. The adverse reactions comprised bradycardia, tachycardia, hypertension, and hypotension.

Statistical analyses

Normally-distributed measurement data are expressed as mean ± standard deviation (SD), and were compared with *t*-test. Count data are expressed as numbers and percentages (n (%)), and were analyzed using chi-square test. All statistical processing was carried out with SPSS 21.0 software, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for preparation of images. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Patients' characteristics

There were no significant differences in sex ratio, mean age, body mass index (BMI) value, height, or ASA categorization (I/II) amongst the four groups ($p > 0.05$; Table 1).

MOAA/S scores and BIS in patients with remimazolam

The MOAA/S score was positively correlated with BIS, and the higher the anesthetic dose, the higher the MOAA/S score and BIS values of the patients. These data are shown in Figure 1.

Systolic blood pressure, diastolic blood pressure, heart rate, and SpO_2 levels

At T2, systolic blood pressure, diastolic blood pressure, heart rate, and SpO_2 were significantly greater in groups R1, R2, and R3 than in the propofol group ($p < 0.05$; Table 2).

PAW and PET_{CO2} levels at different time points

At T3, the PAW values in groups R1 and R2 were significantly greater than those in the propofol group, whereas the PAW values in group R3 were significantly lower. The PET_{CO2} levels in the four groups were significantly higher at T3 than at T1 ($p < 0.05$; Table 3).

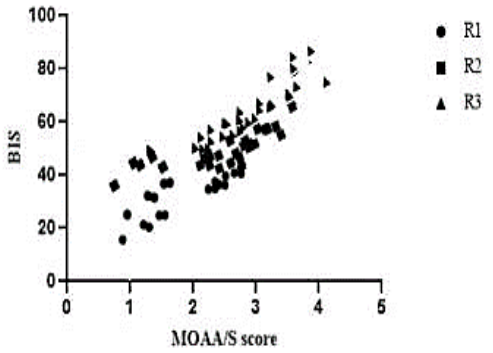

Figure 1: Correlation between MOAA/S scores and BIS in three groups of patients given different doses of remimazolam for induction of general anesthesia

Table 1: Comparison of general information of the four groups

Parameter	Propofol group	R1	R2	R3
Sex ratio (male/female)	17/13	15/15	16/14	14/16
Mean age (years)	61.33±2.79	61.32±2.75	61.27±2.81	61.34±2.76
BMI	22.35±1.72	22.34±1.71	22.37±1.69	22.39±1.70
Height (cm)	167.23±6.59	166.76±6.55	167.11±6.62	167.33±6.45
ASA	18/12	17/13	16/14	15/15

Table 2: Comparison of systolic blood pressure, diastolic blood pressure, heart rate, and SpO_2 levels in the four groups

Group	Time point	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (time)	SpO_2 (%)
Propofol	T1	118.27±10.28	93.88±6.75	72.55±7.23	98.13±1.13
	T2	95.33±9.21*#	77.27±5.11*#	62.88±5.61*#	81.27±1.35*#
	T3	117.11±11.11	92.33±5.46	79.35±6.92	89.33±1.27
R1	T1	119.27±10.15	93.25±7.61	71.89±7.43	98.27±1.25
	T2	105.33±9.25*#	84.33±6.14*#	77.52±6.51*#	93.88±1.05*#
	T3	121.32±11.52	96.27±4.98	77.93±7.15	96.35±1.13
R2	T1	120.02±10.17	94.89±7.96	72.01±7.11	98.14±1.22
	T2	105.52±9.33*#	83.25±6.37*#	77.79±6.41*#	92.33±1.02*#
	T3	118.27±9.15	94.62±4.75	78.02±7.02	96.89±1.12
R3	T1	121.53±9.58	95.88±6.21	72.95±7.12	98.11±1.21
	T2	105.78±9.75*#	84.02±5.01*#	77.35±8.01*#	89.51±1.05*#
	T3	119.33±10.09	97.02±4.93	78.03±7.21	89.33±1.14

*$P < 0.05$, T2 compared with T1 within this group; #$p < 0.05$, T2 in each group compared with T2 of propofol group

Table 3: Comparison of PAW and PETCO2 levels amongst the four groups at different time points

Group	Time point	PAW (cmH_2O)	PET_{CO2}
Propofol	T1	13.33 ±0.51	31.72±5.03
	T2	21.55±0.69	37.88±6.21
	T3	18.41±0.71*#	48.29±6.35*
R1	T1	13.27±0.49	31.88±5.02
	T2	17.35±0.42	37.25±6.61
	T3	21.55±0.59*#	49.51±7.71*
R2	T1	13.28±0.52	32.33±5.11
	T2	18.41±0.61	38.25±6.37
	T3	20.22±0.47*#	49.66±7.52*
R3	T1	13.31±0.48	31.65±5.11
	T2	21.66±0.71	38.77±6.73
	T3	16.33±0.37*#	50.07±6.81*

*P < 0.05, T3 compared with T1 within this group; #p < 0.05, T3 in each group compared with T3 in the propofol group

BCS scores

The BCS scores in the propofol, R1, R2 and R3 groups were 2.88 ± 0.23, 2.27 ± 0.12, 2.31 ± 0.15 and 3.45 ± 0.3, respectively. The BCS and Ramsay scores in the propofol group were significantly higher than those in the R1 and R2 groups, but significantly lower than those in the R3 group (p < 0.05; Figure 2).

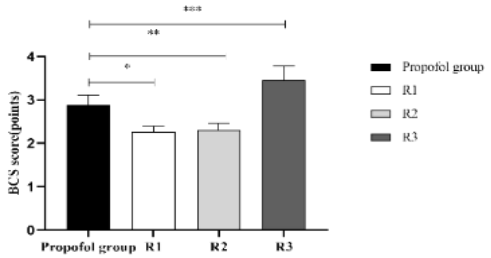

Figure 2: Comparison of BCS scores of the four groups. The BCS scores of the propofol group, R1 group, R2 group, and R3 group were 2.88 ± 0.23, 2.27 ± 0.12, 2.31 ± 0.15, and 3.45 ± 0.33, respectively. *P < 0.001, BCS score in propofol group vs BCS scores in R1 group; **p < 0.001, BCS score in propofol group vs BCS score in R2 group; ***p < 0.001, BCS score in propofol group vs BCS score in R3 group

Ramsay scores

Ramsay scores were 4.21 ± 0.28, 3.05 ± 0.11, 3.51 ± 0.18, and 5.37 ± 0.36 in the propofol, R1, R2, and R3 groups, respectively. Ramsay score in the propofol group was significantly greater than the corresponding scores in groups R1 and R2, but significantly lower than that of group R3 (p < 0.05; Figure 3).

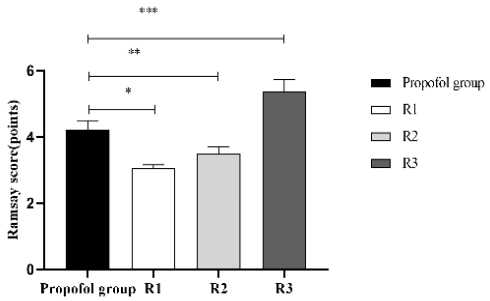

Figure 3: Comparison of Ramsay scores amongst the four groups. The Ramsay scores of the propofol group, R1 group, R2 group, and R3 group were 4.21 ± 0.28, 3.05 ± 0.11, 3.51 ± 0.18, and 5.37 ± 0.36, respectively. *P < 0.001, Ramsay score of propofol group vs that of R1 group; **p < 0.001, Ramsay score of propofol group vs that of R2 group; ***p < 0.001; Ramsay score of propofol group vs that of R3 group

Incidence of adverse reactions

The propofol group had a significantly higher incidence of bradycardia and hypotension than groups R1, R2, and R3 (p < 0.05; Table 4).

Table 4: Comparison of the incidence of adverse reactions among the four groups (n = 30)

Group	Bradycardia	Tachycardia	Hypertension	Hypotension
Propofol	23.33% (7/30)	0.00% (0/30)	0.00% (0/30)	26.6% (8/30)
R1	0.00% (0/30)*	0.00% (0/30)	0.00% (0/30)	0.00% (0/30)#
R2	0.00% (0/30)*	0.00% (0/30)	0.00% (0/30)	0.00% (0/30)#
R3	3.33% (1/30)*	0.00% (0/30)	0.00% (0/30)	6.67% (2/30)#

*P < 0.05, incidence of bradycardia in each group compared with that in the propofol group; #p < 0.05, incidence of hypotension in each group compared with that in the propofol group

DISCUSSION

Anesthetic drugs effectively suppress the central nervous system, thereby producing a sedative-hypnotic effect and ensuring smooth surgery [10]. Studies have found strong fluctuations in patient hemodynamics during general anesthesia, and the fluctuations were attributed to activation of the hypothalamic-pituitary-adrenocortical system and the blue dot-sympathetic-adrenomedullary system by certain doses of anesthetic drugs. This inhibits vasodilation and leads to increased blood pressure and increased heart rate in a short period of time [11]. The induction of general anesthesia requires proper doses of anesthetic medicines in order to ensure an uncomplicated operation and improvement of the postoperative quality of life of the patient. The use of propofol in older people is limited due to its suppression of the respiratory and circulatory systems, as well as high prevalence of severe events e.g. cardiac arrest [2]. Midazolam has a slow onset of action and a long recovery time, and a predisposition to transient paracrine memory loss in patients. Etomidate suppresses adrenocortical function and predisposes patients to postoperative adverse effects such as nausea and vomiting, which limit its use for anesthesia maintenance [7]. Remimazolam, a new type of anesthetic drug with a high safety profile, has a minimal effect on the patient's circulatory breathing and only causes a slight increase in heart rate after administration.

This study found that MOAA/S scores were positively correlated with BIS: the higher the anesthetic dose, the higher the patient's MOAA/S score and BIS value. Since the anesthetic dose in group R3 was significantly higher than those in groups R1 and R2, the results suggest that BIS was significantly correlated with drug dose and MOAA/S score. In addition, the systolic blood pressure, diastolic blood pressure, heart rate, and SpO_2 at T2 were significantly higher in groups R1, R2, and R3 than in the propofol group, indicating that remimazolam at doses between 0.2 and 0.4 mg/kg exerted less hemodynamic effects on the patients, which also suggests that the anesthetic effect of remimazolam was superior to that of propofol. This may be due to the fact that the peak time for plasma concentration of remazolam is about 1 min, its pharmacokinetics is linear, and its clearance is independent of body weight. Esterase is rapidly hydrolyzed and metabolized to zolampropionic acid without pharmacological activity. Thus, is characterized by rapid drug effect, short elimination half-life, short maintenance time, absence of accumulation, and rapid recovery of patients. In addition, it has been reported that the time-dose-related half-life is not affected by infusion time; long-term or high-dose administration does not cause drug accumulation, and increasing the dose within the range of 0.075 - 0.3 mg/kg gradually deepens the degree of sedation [12].

It has been clinically reported that PAW is closely related to the depth of anesthesia. Thus, a shallow depth of anesthesia may lead to insufficient relaxation of body muscles, resulting in increased PAW [5]. In the present study, the PAW values at T3 in groups R1 and R2 were significantly higher than those in the propofol group, while the PAW values at T3 in group R3 were significantly lower than those in the propofol group. All four groups showed significantly higher PET_{CO2} levels at T3 than at T1, indicating that remimazolam produced a better anesthesia outcome than propofol, and it had a less negative impact on respiratory function. The possible explanation is that remimazolam has a less inhibitory effect on respiration and circulation, and less effect on spontaneous respiration and tidal volume. In addition, in a study, colonoscopy under remimazolam sedation maintained a stable state of respiratory function in patients, hypoxemia was effectively relieved by lifting the mandible, and there were no salvage measures such as mechanical and artificial ventilation [7]. Compared with dexmedetomidine and midazolam, remimazolam has less effect on the respiratory system. Within the range of appropriate sedation, the possibility of remimazolam causing respiratory depression is close to zero, even in the case of overdose. When severe respiratory depression occurs, the effect of flumazenil may also be reversed, thereby improving the simplicity of operation and controllability by anesthesiologists, and reducing the difficulty of airway management [6].

The BCS score and Ramsay score were significantly higher in the propofol group than in R1 and R2 groups, but significantly lower than the corresponding scores in group R3, suggesting that remimazolam produced more enrichment in terms of sedation index and comfort of the patients than propofol. There were higher incidents of bradycardia and hypotension in the propofol group than in the other three groups, which is consistent with the findings in a previous study. The above results confirm the high safety profile of remimazolam. In particular, the current study also found that remimazolam at a dose of 0.3 mg/kg was associated with more rapid induction of anesthesia than at a dose of 0.2 mg/kg, and a

less hemodynamic impact and higher safety than a dose of 0 .4 mg/kg. Postoperative recovery from anesthesia relies mainly on the metabolism of the anesthetic agent in the body [8]. Antagonists are introduced for patients with slow metabolism due to impairment of liver and kidney function and for those with preoperative anemia or hypoproteinemia.

Clinical research areas of high priorities center on the pharmacokinetics of new drugs, more precise dose design for multiple diseases, and novel delivery techniques for improving bioavailability. Pterostilbene (PTER) is a newly recognized phytoestrogen with confirmed anticancer, antioxidant, and anti-inflammatory effects [13]. High doses of PTER have been utilized in animals in certain research with no apparent hazardous side effects, and animal trials have shown considerable improvements in learning and memory function in aged rats. A large corpus of experimental data confirms the neuroprotective effects of estrogens, especially in the brain and neural tissue due to activation of the MAPK/ERK signal pathway [14]. In mammals, there are three major MAPK pathways in which phosphorylation of key molecules mediates the activation of the MAPK signal pathway. The MAPK/ERK1/2 signal pathway is involved in the regulation of cellular responses, including cell proliferation, cell migration, cell differentiation, and cell regulation. In a study, the expression of p-ERK1/2 was significantly upregulated after PTER pre-treatment, and cell survival was significantly improved, suggesting that PTER also exerts neuroprotective effects by activating the MAPK/ERK1/12 signal pathway. Furthermore, activin A has been proven to produce neuroprotective benefits, while Emodin, a powerful monomer produced from the Chinese plant rhubarb, has greater biological activity. Emodin functions as a neuroprotective agent by acting as an antioxidant and inhibiting glutamate damage [15]. A high expression level of activin has been reported in the medium of pc-12 cells pre-treated with Emodin and then subjected to oxygen-glucose surplus. This suggests that Emodin may, in one way or another, pre-activate some self-protective mechanisms in neuronal cells, resulting in upregulation of activin expression in neuronal cells. It has been hypothesized that Emodin may pre-activate the Activin A/Smads signal system through some therapeutic targets and that through a positive feedback mechanism, it continuously modulates autocrine Activin A protein to protect neuronal cells against injury [16]. Thus, the neuroprotective effect of Emodin may be mediated by counteracting post-injury cell death.

Limitations of the study

However, there are some limitations in the present study. For starters, the experimental sample was small. This may have skewed the results. Secondly, the modified MOAA/S scale which is usually employed in sedation-related medication and device research was not used to measure the levels of sedation in patients. The fundamental disadvantage of MOAA/S lies in its inability to identify the severity of general anesthesia. Moreover, the present MOAA/S scale has significant limitations in the assessment of the whole clinical state of the sedation continuum. Thus, the Extended Observer Assessment of Alertness and Sedation (EOAA/S) should be adopted for assessment in subsequent studies.

CONCLUSION

The use of remimazolam for general anesthesia at a dose of 0.3 mg/kg produces a promising sedation outcome and a high safety profile, with no significant adverse impact on respiratory function and hemodynamics. However, further clinical trials are required prior to its application in clinical practice.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study protocol was approved by the Hospital Ethics Committee of Handan Central Hospital (approval no. Gh-ju20190408).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. Zhijie Liu drafted and revised the manuscript. Xing Zhao, Yongxue Chen, and Yang Gao conceived and designed this study, and was in charge of syntax modification and revision of the manuscript. All the authors read and approved the final version of the manuscript.

REFERENCES

1. *Sadee W. Gene-gene-environment interactions between drugs, transporters, receptors, and metabolizing enzymes: Statins, SLCO1B1, and CYP3A4 as an example. J Pharm Sci 2013; 102(9): 2924-2929.*
2. *Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. J Anesth 2020; 34(4): 543-553.*
3. *Kleiman RB, Darpo B, Thorn M, Stoehr T, Schippers F. Potential strategy for assessing QT/QTc interval for drugs that produce rapid changes in heart rate: Electrocardiographic assessment of the effects of intravenous remimazolam on cardiac repolarization. Br J Clin Pharmacol 2020; 86(8): 1600-1609.*
4. *Wang F, Zhou Q, Shen M, Quan J, Chen J, Shi J, Zou X. Efficacy and safety of remimazolam in procedural sedation and analgesia: A protocol for systematic review a meta-analysis. Medicine (Baltimore) 2020; 99(27): e20765.*
5. *Khan AI, Fischer M, Pedoto AC, Seier K, Tan KS, Dalbagni G, Donat SM, Arslan-Carlon V. The impact of fluid optimization before induction of anesthesia on hypotension after induction. Anesthesia 2020; 75(5): 634-641.*
6. *Poterman M, Kalmar AF, Buisman PL, Struys MMRF, Scheeren TWL. Improved hemodynamic stability and cerebral tissue oxygenation after induction of anesthesia with sufentanil compared to remifentanil: a randomized-controlled trial. BMC Anesthesiol 2020; 20(1): 258.*
7. *Aguilera R, Sinclair M, Valverde A, Bateman S, Hanna B. Dose and cardiopulmonary effects of propofol alone or with midazolam for induction of anesthesia in critically ill dogs. Vet Anaesth Analg 2020; 47(4): 472-480.*
8. *Bonnet MP, Mercier FJ, Vicaut E, Galand A, Keita H, Baillard C; CAESAR working group. Incidence and risk factors for maternal hypoxemia during induction of general anesthesia for non-elective Caesarean section: a prospective multicentre study. Br J Anaesth 2020; 125(1): e81-e87.*
9. *Ferreira AL, Nunes CS, Vide S, Felgueiras J, Cardoso M, Amorim P, Mendes J. Performance of blink reflex in patients during anesthesia induction with propofol and remifentanil: prediction probabilities and multinomial logistic analysis. Biomed Eng Online 2020; 19(1): 84.*
10. *Dhande K, Kshirsagar J, Dhande A, Patil N, V P Jr. Hemodynamic stability, patient acceptance and cost of intravenous propofol and inhalational sevoflurane for induction of anesthesia: A prospective, randomized comparative study. Cureus 2020; 12(4): e7687.*
11. *Maitra S, Baidya DK, Anand RK, Subramanium R, Bhattacharjee S. Carotid artery corrected flow time and respiratory variations of peak blood flow velocity for prediction of hypotension after induction of general anesthesia in adult patients undergoing elective surgery: A prospective observational study. J Ultrasound Med 2020; 39(4): 721-730.*
12. *Yoon U, Setren A, Chen A, Nguyen T, Torjman M, Kennedy T. Continuation of angiotensin-converting enzyme inhibitors on the day of surgery is not associated with increased risk of hypotension upon induction of general anesthesia in elective noncardiac surgeries. J Cardiothorac Vasc Anesth 2021; 35(2): 508-513.*
13. *LaGrew JE, Olsen KR, Frantz A. Volatile anaesthetic for treatment of respiratory failure from status asthmaticus requiring extracorporeal membrane oxygenation. BMJ Case Rep 2020; 13(1): e231507.*
14. *Stockton DW, Kishnani P, van der Ploeg A, Llerena J Jr, Boentert M, Roberts M, Byrne BJ, Araujo R, Maruti SS, Thibault N, et al. Respiratory function during enzyme replacement therapy in late-onset Pompe disease: longitudinal course, prognostic factors, and the impact of time from diagnosis to treatment start. J Neurol 2020; 267(10): 3038-3053.*
15. *Shibuta H, Yamana R, Kashimoto J, Kamio K, Suda A. Comparison of the anesthetic effect by the injection route of mixed anesthesia (medetomidine, midazolam and butorphanol) and the effect of this anesthetic agent on the respiratory function. J Vet Med Sci 2020; 82(1): 35-42.*
16. *Munaf M, Rajeswari C, Rajaram M, Balachander H. A study on the effect of intraoperative continuous positive airway pressure (CPAP) on postoperative pulmonary function in overweight patients undergoing lower limb, lower abdominal, or vaginal surgeries under spinal anesthesia. Adv Respir Med 2020; 88(3): 176-182.*