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Study of the rational dose of propofol in elderly patients under bispectral index monitoring during total intravenous anesthesia

A PRISMA-compliant systematic review

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Abstract

Background: Propofol has been used widely as an anesthetic for elderly patients; however, the drug instructions only indicate that the need for maintenance of general anesthesia in elderly patients is reduced, and not the extent of the reduction. This study has summarized the usage of propofol in total intravenous anesthesia under bispectral index (BIS) monitoring and determined the optimum dosage of propofol for elderly patients.

Methods: The study comprised 156 patients undergoing elective surgery under general anesthesia divided into 2 groups according to their age: the elderly group (O group) and nonelderly group (Y group). BIS monitoring was used in both groups during the operation, and propofol and remifentanil were used to maintain anesthesia. The preoperative special conditions, intraoperative maintenance of propofol, remifentanil, fentanyl, cis-atracurium, vasoactive drug use, and hemodynamic changes were summarized.

Results: Propofol maintenance in the O group was 3.372 ± 0.774 mg/(kg h), which was significantly lesser than that in Y group ($P < 0.05$). The incidence of cardiovascular and cerebrovascular diseases and the use rate of vasoactive drugs in the O group were significantly higher than in the Y group ($P < 0.05$).

Conclusion: Propofol maintenance in the O group was significantly lower than that in the nonelderly group; this indicates that the anesthetic drug delivery rate for elderly patients should be reduced.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, EEG = electroencephalogram, HR = heart rate.

Keywords: elderly, propofol, rational administration, total intravenous anesthesia

1. Introduction

Propofol is an ultrashort-acting intravenous anesthetic with a relatively complex mechanism of action in the central nervous system that interacts with various neurotransmitter receptors.[1] Compared with other anesthetics, propofol has the advantages of rapid onset, short duration of action, and fewer side effects, such as postoperative nausea. It has been widely used as an intravenous anesthetic for elderly patients.[2] However, the current propofol specifications are generic, stating that the average person requires a maintenance drug delivery rate of 4 to 12 mg/(kg h), and that the maintenance rate in elderly patients should be reduced, but do not specify the scope of the reduction. Most of the current studies have only studied the target concentration of propofol effect chambers,[3] without specifying the pump dose. However, in clinical application, only hemodynamic changes are used to adjust the drug delivery rate, which lacks scientific rationale. This study has summarized the maintenance rate of propofol in total intravenous anesthesia under bispectral index (BIS) monitoring and calculated the dosage of propofol for elderly patients to determine the optimum delivery rate of propofol for elderly patients. This study has aimed to provide a scientific rationale for the application of propofol in elderly patients receiving total intravenous anesthesia.

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2. Information and methodology

The ethical approval for this retrospective study was provided by Ethics Committee of the Second Hospital of Jilin University on December 27, 2018. Data and patient identification were processed anonymously before analysis. Data were obtained from the medical records and electronic database of the Second Hospital of Jilin University. The study examined a total of 156 randomly selected patients undergoing surgery under general anesthesia between August, 2017 and April, 2018 in the Second Hospital of Jilin University. The patients had to fulfil the following criteria: age 20 to 85 years of age, weight 40 to 90 kg, and American Society of Anesthesiologists (ASA) grade II to III. Patients were excluded for the following reason: body mass index >30 kg/m^2; operative time more than 8 hours; severe liver and kidney dysfunction; severe circulatory system disease; a history of allergies to psychotropic or anesthetic drugs; and patients with a large intraoperative bleed who required blood transfusion. The patients were divided into 2 groups according to age: elderly group (group O, patients of 65–85 years of age) and the nonelderly group (group Y, patients of 20–64 years of age).

The following procedures occurred: routine mask inhalation of oxygen and monitoring of noninvasive blood pressure, heart rate (HR), electrocardiography, pulse oxygen saturation (SpO_2%), with BIS after entering the room, and continuous monitoring of invasive blood pressure. For open peripheral venous access, penehyclidine 1 mg was administered. To induce rapid intravenous general anesthesia, midazolam (0.05 mg/kg), fentanyl (4.0 μg/kg), etomidate (0.2 mg/kg), and cis-atracurium (0.15 mg/kg) were applied. After the patient lost consciousness, the BIS value decreased to 40 to 60, and spontaneous respiration did not occur; the patients were given mask assisted ventilation. After the drug was completely effective, a tracheal intubation was performed. After successful intubation, the anesthetic machine was connected to perform mechanical ventilation with pure oxygen. The tidal volume was 8 to 10 mL/kg, the ventilation frequency was 12/min, the oxygen flow rate was 2 L/min, and the inspiratory expiratory ratio was 1:2.

Both groups were treated with pumping propofol and remifentanil, and intermittent injection of cis-atracurium and fentanyl to maintain anesthesia. The initial pump velocity of remifentanil was 15 μg/(kg h), and the propofol injection rate was 5 mg/(kg h), which was increased or decreased to maintain a BIS value of 40 to 60. The anesthetic machine parameters were adjusted to maintain an end expiratory partial pressure of carbon dioxide ($P_{ET}CO_2$) value of 35 to 45 mm Hg. The hemodynamic fluctuation of the 2 groups was controlled to within ±30% of the basic value by the proper use of vasoactive drugs, based on the changes in the circulatory system during the operation. At the end of the operation, the infusion of anesthetic drugs was stopped. When the patient awoke, spontaneous respiration was resumed, and the extubation conditions were satisfied, the tracheal catheter was removed and the patient was placed in the postanesthesia care unit.

The SPSS19.0 software package was used for statistical analysis. If quantitative data conformed to normal distribution, they were expressed as the mean ± standard deviation, and statistical analysis used an independent-sample *t* test or a corrected *t* test; if the data were not normal, the rank sum test was used. Count data were expressed as a percentile (rate) and analyzed by the chi-square test. A value of $P<0.05$ was considered to be statistically significant.

3. Results

Our study included 156 patients—elderly patients (group O, n=70) and nonelderly patients (group Y, n=86). To avoid bias of the results, there were no significant differences in sex, height, weight, operative time, anesthetic time, surgical classification (Table 1), intraoperative anesthesia maintenance of remifentanil (R), cis-atracurium (H), and fentanyl (F) (Table 2), intraoperative infusion volume, and urine volume (Table 3), the maintenance dose of propofol in ASA III in each group (Table 4), the use of vasoactive drugs (norepinephrine, urapidil, esmolol, and atropine) between groups (Table 5) (all $P>0.05$). There were no significant differences in mean arterial pressure, HR, SpO_2, BIS, and other vital signs at any time point (the time of room entry [T0], preinduction [T1], intubation [T2], beginning of operation [T3], end of operation [T4], extubation [T5]) (Tables 6–9) (all $P>0.05$). The incidence of hypertension, heart disease, diabetes, and cerebrovascular diseases were significantly different between the 2 groups (Table 10) ($P<0.05$). The maintenance dose of propofol in the O group was significantly lower than that in the Y group (Fig. 1) ($P<0.05$). The maintenance dose of propofol in the O group was significantly lower than that in the Y group in ASA II (Table 4) ($P<0.05$). There were significant differences in ASA grading and ephedrine use ($P<0.05$).

Table 1

Comparison of general conditions in each groups.

	O group (n=70)	Y group (n=86)	*P*
Sex (M:F)	32:38	27:59	0.067
Stature (cm)	163.37±7.201	163.49±5.841	0.729
Weight (kg)	63.03±11.440	63.75±9.439	0.665
Operative time (h)	2.19±1.183	1.87±1.012	0.092
Anesthesia time (h)	2.65±1.186	2.37±1.158	0.111
ASA (II:III)	29:41	75:11	<0.01
Surgical classification			0.289
Surface surgery	18	32	_
Laparoscopic surgery	17	18	_
Laparotomy	15	16	_
Laparotomy+laparoscopic surgery	15	7	_
Thoracoscopy	2	7	_
Open-chest	3	6	_

Data shown as mean±standard or number.
ASA=American Society of Anesthesiologists, O group=elderly group, Y group=the nonelderly group.

Table 2

Comparison of anesthesia maintenance drugs in each group.

Maintenance medication	O group (n=70)	Y group (n=86)	*P*
B (mg/kg/h)	3.372±0.774	3.701±0.862	0.005
R (μg/kg/h)	11.68±2.477	11.85±2.624	0.355
H (mg)	21.29±8.253	22.55±23.581	0.411
F (mg)	0.2486±0.088	0.2279±0.081	0.145

Data shown as mean±standard.
B=intraoperative anesthesia maintenance of propofol, F=intraoperative anesthesia maintenance of fentanyl, H=intraoperative anesthesia maintenance of benzoxanthine atracurium, O group=elderly group, R=intraoperative anesthesia maintenance of remifentanil, Y group=the nonelderly group.

Table 3

Comparison of intraoperative infusion volume and urine volume.

	O group (n=70)	Y group (n=86)	*P*
Infusion volume (mL)	1005.71±606.937	857.56±546.406	0.113
Urine (mL)	200.71±162.956	155.52±141.134	0.150

Data shown as mean±standard.
O group=elderly group, Y group=the nonelderly group.

Table 4

Comparison of the maintenance dose of propofol in different American Society of Anesthesiologists grading in each group (mg/[kg h]).

ASA	O group (n=70)	Y group (n=86)	*P*
II	3.333±0.951	3.694±0.864	0.015
III	3.400±0.631	3.753±0.894	0.198

Data shown as mean±standard.
ASA=American Society of Anesthesiologists, O group=elderly group, Y group=the nonelderly group.

Table 5

Comparison of intraoperative use of vasoactive drugs in each group.

Vasoactive drug	O group (n=70)	Y group (n=86)	*P*
Ephedrine	39 (55.7%)	30 (34.9%)	0.009
Norepinephrine	9 (12.9%)	10 (11.6%)	0.815
Urapidil	6 (8.6%)	4 (4.7%)	0.320
Esmolol	0	2 (2.3%)	0.199
Atropine	4 (5.7%)	5 (5.8%)	0.979

Data shown as percentage or number.
O group=elderly group, Y group=the nonelderly group.

Table 6

Comparison of mean arterial pressure in each group at different time points.

Time point	O group (n=70)	Y group (n=86)	*P*
T0	115.6±17.15	109.64±15.91	0.026
T1	109.20±13.90	107.23±16.31	0.424
T2	76.10±15.09	80.37±16.47	0.104
T3	76.65±13.51	73.55±12.38	0.116
T4	86.81±13.62	84.48±14.89	0.209
T5	103.73±17.94	99.64±18.08	0.192

Data shown as mean±standard.
O group=elderly group, T0=the time of room entry, T1=the time of preinduction, T2=the time of intubation, T3=the time of the beginning of operation, T4=the time of the end of operation, T5=the time of extubation, Y group=the nonelderly group.

4. Discussion

Owing to the rapidly aging population of China, more elderly patients require surgical treatment. The elderly are often accompanied by a variety of major organ dysfunction and associated diseases, which results in changes in the pharmacodynamics and pharmacokinetics of drugs, increased sensitivity to central inhibitory drugs,[4] and surgical stimulation. In addition, the hemodynamics in elderly patients fluctuates greatly during the perioperative period. There were significant differences in the cardiovascular and cerebrovascular diseases, and diabetes between the 2 aged groups, which was also reflected in the ASA classification. Therefore, the anesthesia of elderly patients may lead to a variety of adverse reactions during the induction of anesthesia, and during and after the operation, which may seriously affect the physical and mental health of elderly patients, endanger their lives and safety, and increase the risks associated with the surgery.

Propofol has been used widely in clinical practice because of its advantages of short duration of action, quick recovery, and reduced postoperative nausea and vomiting. However, because of its limited cardiac contractility,[5,6] it can lead to obvious dilation of blood vessels, reduction in the tension of blood vessels,

Table 7

Comparison of heart rate in each group at different time points.

Time point	O group (n=70)	Y group (n=86)	*P*
T0	75.73±12.060	81.28±15.143	0.014
T1	74.56±11.722	81.22±14.969	0.003
T2	73.09±14.092	80.78±14.768	0.001
T3	64.21±12.187	64.60±11.354	0.700
T4	63.60±12.309	65.10±13.141	0.487
T5	85.07±14.926	84.79±16.237	0.911

Data shown as mean±standard.
O group=elderly group, T0=the time of room entry, T1=the time of preinduction, T2=the time of intubation, T3=the time of the beginning of operation, T4=the time of the end of operation, T5=the time of extubation, Y group=the nonelderly group.

Table 8

Comparison of pulse oxygen saturation in each group at different time points.

Time point	O group (n=70)	Y group (n=86)	*P*
T0	96.76±1.628	97.03±1.850	0.256
T1	96.56±2.375	97.22±1.856	0.079
T2	99.57±0.809	99.35±1.003	0.175
T3	99.74±0.530	99.60±0.580	0.079
T4	99.89±0.363	99.70±0.753	0.114
T5	99.49±1.225	99.24±1.363	0.205

Data shown as mean±standard.
O group=elderly group, T0=the time of room entry, T1=the time of preinduction, T2=the time of intubation, T3=the time of the beginning of operation, T4=the time of the end of operation, T5=the time of extubation, Y group=the nonelderly group.

Table 9

Comparison of bispectral index values in each group at different time points.

Time point	O group (n=70)	Y group (n=86)	*P*
T0	95.10±3.584	95.31±3.555	0.673
T1	94.56±3.991	95.40±2.952	0.389
T2	38.84±9.495	42.90±11.131	0.020
T3	46.47±8.182	47.53±11.789	0.677
T4	58.04±9.905	60.97±10.452	0.077
T5	80.64±7.333	81.24±4.973	0.604

Data shown as mean±standard.
O group=elderly group, T0=the time of room entry, T1=the time of preinduction, T2=the time of intubation, T3=the time of the beginning of operation, T4=the time of the end of operation, T5=the time of extubation, Y group=the nonelderly group.

Table 10

Comparison of the incidence of special cases before operation in each group.

Preoperative special circumstances	O group (n=70)	Y group (n=86)	*P*
Hypertension	24 (34.3%)	16 (18.6%)	0.026
Heart disease	21 (30.0%)	8 (9.3%)	0.001
Diabetes	14 (20.0%)	6 (7.0%)	0.016
Cerebrovascular disease	9 (12.9%)	3 (3.5%)	0.029

Data shown as percentage or number.
O group=elderly group, Y group=the nonelderly group.

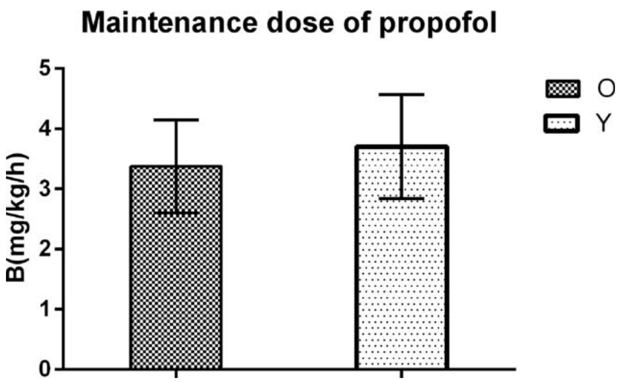

Figure 1. The maintenance dose of propofol in the 2 groups.

reduction in the venous reflux, and induction of hypotension. Therefore, it is necessary to pay attention to its usage and dosage in elderly patients.[7]

Many experiments have confirmed that accurate anesthesia depth monitoring can not only effectively avoid intraoperative awareness caused by insufficient anesthesia effect and severe complications caused by anesthetic overdose,[8–10] but also improve the quality of anesthesia.[11] The BIS, as an electroencephalogram (EEG) quantification parameter, is sensitive for the prediction of body motion and intraoperative awareness through monitoring the changes in the state of the cerebral cortex, and offers an excellent representation of the depth of anesthesia,[12,13] and has emerged as a key means of monitoring depth of anesthesia in recent years.[14] There is a good correlation between BIS and the drug action on the cerebral cortex,[15,16] allowing accurate reflection of the depth of anesthesia, especially the sedation depth of simple propofol general anesthesia.[3,15,17] As the depth of sedation of propofol deepens, consciousness gradually disappears,[18] and the BIS value decreased, with an increase in the target control concentration and sedation, which was well correlated with the observer's assessment of alertness/sedation score (OAA/S).[19] Therefore, BIS is an appropriate reflection of the depth of propofol sedation.

Propofol metabolism may be affected by age, sex, weight, and ethnicity, with age being an important factor. Previous research has mainly examined adults,[20] with 2 studies that have shown that the pharmacokinetics of propofol vary with age.[21] Moreover, Schnider et al[22] studied the effect of age on the efficacy of propofol and the equilibrium time of the plasma effect sites. They found that steady-state plasma C50 during waking and EEG-activated C50 reflected brain sensitivity, both of which increased the sensitivity of elderly patients to the effects of propofol. These findings suggested that the amount of propofol used in elderly patients should be reduced for pharmacokinetic and pharmacodynamic reasons.[22] A study showed that propofol clearance was negatively correlated with central volume and age in patients over 60 years of age,[23] and that older patients have reduced tolerance and demand for anesthetics. The change in anesthetic demand paralleled the loss rate of cortical neurons, the decrease in the rate of cortical neuron density,[24] the absolute value in the decrease of cerebral metabolic rate and cerebral blood flow, and also the decline of neurotransmitter activity and related receptors related that occur with aging.[25,26] From the results of this study, it can clearly be seen that the BIS value at the time of intubation in elderly patients was significantly lower than that of nonelderly patients ($P < 0.05$).

There was no statistical difference between the 2 groups in the induction of general anesthesia and maintenance of other drugs in this experiment. On this basis, the pump dose of propofol during the maintenance was studied in detail. The result was 3.372 ± 0.774 mg/(kg h) in the O group, which was significantly lower than in the Y group (3.701 ± 0.862 mg/[kg h]). The maintenance dose of propofol was 3.333 ± 0.951 mg/(kg h) in ASA II in O group, which was significantly lower than in the Y group (3.694 ± 0.864 mg/[kg h]). The maintenance dose of propofol was 3.400 ± 0.631 mg/(kg h) in ASA III in O group, which was lower than in the Y group (3.753 ± 0.894 mg/[kg h]), but there was no significant difference in 2 groups. Because elderly patients have more underlying diseases, lower vascular elasticity, and greater sensitivity to drugs than nonelderly patients, their vital signs fluctuate greatly during the operation. The blood pressure and HR of the O group at the time of entering the room were significantly different from those of the Y group. The utilization rate of ephedrine during operation was significantly higher in the O group than the Y group, which also led to a significant difference in HR between the 2 groups before induction and during intubation. However, the vital signs were stable during the operation, with no significant difference between groups. Remifentanil combined with propofol can also reduce the BIS value in sedation.[27,28] As there was no significant difference in the use of remifentanil in this experiment, the change in BIS value would not have been affected. From the results of this study, it can be seen that the maintenance dose of propofol in elderly patients was significantly lower than that of nonelderly patients ($P < 0.05$). The optimal dosage of propofol was 3.372 ± 0.774 mg/(kg h), after the removal of all interfering factors during the operation.

The disadvantage of this study is primarily that, although the same anesthesiologist conducted the procedure, the rate of administration may vary with each induction, thus increasing the risk of bias. Second, with regard to the comparability and standardization of the study group, the retrospective design of the study may increase the risk of bias. Finally, the number of patients undergoing thoracoscopic and thoracotomy was small and there is no in-depth study of the effects of single-lung ventilation on BIS, which may also bias the results.

5. Conclusions

The reasonable dose of propofol for the maintenance of elderly patients with intravenous anesthesia under BIS was 3.372 ± 0.774 mg/(kg h). Compared with nonelderly patients, a lower dosage could maintain better anesthesia.

Author contributions

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Funding acquisition: Lina Jia, Tongwei Yang.
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