Treatment of different-aged children under bispectral index monitoring with intravenous anesthesia with propofol and remifentanil

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Abstract. – OBJECTIVE: To investigate the changes in bispectral index (BIS) to determine the controllability and safety of intravenous anesthesia with propofol and remifentanil in different-aged children.

PATIENTS AND METHODS: Forty cases of ASA levels I or II were divided into four groups (A group, ≤ three months old; B group, three months to two years old; C group, two years to six years old; and D group, six years to 12 years old) with 10 cases in each group. Propofol and remifentanil were used in anesthesia induction and maintenance. Hemodynamic changes, BIS values, and sedation scores during T1, T2, T3, T4, T5, T6, and T7, as well as spontaneous breathing recovery and extubation times, were recorded.

RESULTS: Compared with that at T1, the BIS values at T2, T3, T4, T5, and T6 decreased ($p < 0.01$). SBP, DBP, and HR also decreased ($p < 0.01$). Compared with the other groups, the extubation time of A group increased ($p < 0.01$). At T2, T3, T4, T5, T6, and T7, the BIS values of A group were all less than those of C group ($p < 0.01$).

CONCLUSIONS: Anesthesia is stable and safe when the same unit doses of propofol and remifentanil are administered to different-aged children. In infants under three months, the BIS values were lower, with prolonged palinesthesia time.

Key Words:
Propofol, Remifentanil, Bispectral index child sedation score.

Introduction

Bispectral index (BIS) has been widely used in clinical anesthesia since it was approved by the Food and Drug Administration for use as an index for monitoring anesthesia depth and sedation level in 1998. BIS can reflect the electrical activity of the cerebral cortex and the sedative ingredients of anesthesia. The BIS algorithm is based on the comprehensive analysis of the original electroencephalograms (EEG) of adults. However, pediatric brain waves are different from those of adults[1], and pediatric brain development and synapse formation continues until five years of age. Therefore, using adult BIS standards to monitor children results in large deviations. BIS can reflect various anesthesia depths. BIS values from 40 to 60 indicate a moderate hypnotic state, and those below 40 suggest deep hypnotic states[2]. Studies[3] have shown that under the same propofol plasma-effect concentrations, the correlations of BIS values for different-aged children with plasma concentrations were superior to those of adults. At the same plasma concentration, the younger the children are, the higher the BIS values will be. For loss of consciousness and awareness recovery, the BIS values of children are higher than those of adults. Continuous monitoring of blood pressure and BIS while the subject is under the effects of anesthesia could help determine the prevalence of postoperative mortality, because low blood pressure and deep anesthesia (BIS < 45) in adults exhibits some correlation with postoperative recovery and mortality[4–6]. The use of BIS as a means of sedation monitoring of different-aged children, the applicability of BIS to younger children, and whether the application of BIS monitoring could reduce the use of narcotic drugs, shorten extubation and eye opening time, prevent excessive sedation, and affect children's turnover are topics currently under investigation[7].

Propofol is an intravenous anesthetic drug with rapid onset, short half-life, and high controllability. Remifentanil is an opioid drug with an ultra-short acting period, rapid onset, strong analgesic effect, and without *in vivo* accumulative characteristics. These two drugs are widely applied in combination in adults. Recent reports have investigated the safety and effectiveness of propofol and remifentanil anesthesia in scheduled surgeries on children, but few studies have focused on their effects on different age groups, particularly on intraoperative anesthesia monitoring depth in younger children.

In the present study, the anesthesia depth was assessed by observing changes in BIS values for a

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better understanding of the effectiveness, controllability, and safety of intravenous anesthesia with propofol and remifentanil in different-aged children. The effects of intravenous anesthesia with propofol and remifentanil on four groups of children (A group, ≤ three months; B group, three months to two years old; C group, two years to six years old; and D group, six years to 12 years old) were compared. An anesthesia depth monitor was used to record BIS values at different time points, hemodynamic changes, sedation scores, and spontaneous breathing recovery and extubation times to obtain a better understanding of the BIS changes and the effectiveness, controllability, and safety of the same unit dose of propofol and remifentanil anesthesia in different-aged children.

Patients and Methods

General Information

Forty children under scheduled surgery conditions (including chest, abdomen, neurology, orthopedics, and oncology), aged from two months to 12 years old, with ASA Levels I or II, and scheduled for general anesthesia, were divided into four groups (A group, ≤ three months; B group, three months to two years old; C group, two years to six years old; and D group, six years to 12 years old), with 10 cases in each group. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Capital Medical University. Written informed consent was obtained from all participants.

Anesthesia Method

Pethidine and phenobarbital (Shanghai Harvest Pharmaceutical Co., Ltd., Shanghai, China), at a dosage of 1 mg/kg each, were intramuscularly injected 30 min prior to operation. Induced intravenous anesthesia was then performed with 3 mg/kg propofol (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., Beijing, China), 1 g/kg remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China), and 0.1 mg/kg vecuronium (N.V. Organon Company, Oss, Holland). Intubation was performed after 2 min, with the tidal volume of the mechanical ventilation at 10 ml/kg. The respiratory frequency was adjusted to 35 mmHg to 45 mmHg according to the normal pressure of end-tidal carbon dioxide. The anesthesia was maintained via continuous intravenous infusion of remifentanil (0.25 $g\cdot kg^{-1}\cdot min^{-1}$) and propofol (6 $mg\cdot kg^{-1}\cdot h^{-1}$), and maintained supplementally via N_2O-O_2 inhalation. Treatment with all anesthetic drugs was stopped prior to suturing of the skin. Fentanyl intravenous infusion was administered, and then a Funiya continuous analgesia pump (Royal Fornia Medical Equipment Co. Ltd., Zhuhai, China) was used for analgesia with fentanyl (10 $g\cdot kg^{-1}\cdot d^{-1}$, Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) for 48 h. The patients were extubated once they recovered spontaneous breathing.

Monitoring Project

A Hewlett-Packard monitor (Philips Medizin Systeme Böblingen GmbH, Berlin, Germany) was used intraoperatively to continuously monitor SBP, DBP, and HR changes during pre-induction (T1), post-induction (T2), intra-intubation (T3), skin incision (T4), withdrawal time (T5), spontaneous breathing time recovery (T6), and extubation (T7). An Aspect A-2000XP BIS monitor (Aspect Medical Systems Inc., Newton, MA, USA) was used to monitor and record BIS, 95% edge frequency (95% SEF), operation time, withdrawal-spontaneous breathing recovery time, and withdrawal-extubation time. The state of consciousness was assessed using the University of Michigan Sedation Scale (UMSS score): 0, awake or alert; 1 point, mild sedation, fatigue/drowsiness, appropriate response to the surrounding speech and sounds; 2 points, moderate sedation, sleeping, easy to wake by mild tactile stimulation or a simple verbal command; 3 points, deep sedation, deep sleeping, only awakened by important stimuli; and 4 points, could not be woken up. The status of the children was assessed by assigned people with UMSS scores.

Statistical Analysis

SPSS 11.5 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The measurement data were expressed as mean ± standard deviation (±s). The intergroups were compared using one-way ANOVA; intragroup comparisons were conducted using independent sample *t*-test, and $p < 0.05$ was considered statistically significant.

Results

Demographic Characteristics in the Subgroups

The gender, age, weight, and operation time of the patients are shown in Table I. The four

Table I. General information of 4 groups ($\bar{x} \pm s$).

Group	Cases	Gender (male/female)	Age (month/year)	Body weight (kg)	Operation time (min)
A	10	8/2	2.4 ± 0.7 (m)	4.9 ± 0.9	91.4 ± 47.3
B	10	6/4	11.6 ± 9.5 (m)*	9.4 ± 2.0*	111.0 ± 44.8
C	10	6/4	3.8 ± 1.3 (y)*	15.9 ± 2.7*	89.5 ± 59.1
D	10	7/3	9.4 ± 2.2 (y)*	28.8 ± 11.6*	114.0 ± 51.3

Note: Compared with A group, *$p < 0.01$.

groups exhibited statistically significant differences in terms of age and body weight ($p < 0.01$), and no significant differences was found in terms of duration of surgery.

Hemodynamic Changes in the Subgroups

The SBP, DBP, and HR of the four groups decreased significantly ($p < 0.01$) at T2 compared with those at T1, and then increased at T3. No significant difference was found when compared with those at T1. SBP, DBP, and HR returned to their T2 values from T4 to T6 ($p > 0.01$), showing a statistically significant difference with those at T1 ($p < 0.01$). SBP, DBP, and HR increased at T7, with no statistical difference when compared with those at T1.

BIS and 95% SEF Monitoring in the Subgroups

The BIS values of the four groups decreased significantly from T2 to T6, with statistically significant difference when compared with those at T1 ($p < 0.01$). At T7, the BIS value returned to that at T1. The BIS values of A group were less than those of C group from T2 to T6, with statistically significant differences. At T7, the BIS value of A group was less than those of C and D groups. The 95% SEF values of A group from to T6 significantly decreased compared with that at T1, and then returned at T7. By contrast, the 95% SEF values of B, C, and D groups did not change significantly. The 95% SEF values of A group from T2 to T6 were significantly lower than those of the other groups (Table II; $p < 0.01$).

Recovery Data from Anesthesia in the Subgroups

No statistically significant differences were found among the four groups in terms of spontaneous breathing recovery time. A group had a significantly longer extubation time than the other groups ($p < 0.01$). The difference in extubation time between the B and C groups was significant (Table III; $p < 0.05$).

UMSS Scores in the Subgroups

At T1, all the children were awake, so UMSS scores were 0 point to 1 point. The UMSS scores at T3 were 4 points, and returned to 0 point to 1 point at T7.

Discussion

This study assessed the anesthesia depth by observing variations in BIS values to better understanding the effectiveness, controllability, and safety of intravenous anesthesia using propofol and remifentanil in different-aged children. The results show that compared with that at T1, the BIS values from T2 to T6 decreased ($p < 0.01$). SBP, DBP, and HR also decreased ($p < 0.01$). A group also had the longest extubation time ($p < 0.01$). The BIS values of A group were less than those of C group from T2 to T6 ($p < 0.01$). At T7, the BIS values of A group were less than those of C and D groups ($p < 0.05$).

BIS monitoring is the only tool used to monitor the anesthesia depth in children[8]. It could perform stepwise regression analysis of the EEG

Table II. Withdrawal situation of the 4 groups ($\bar{x} \pm s$).

	A	B	C	D
Withdrawal to spontaneous breathing recovery (min)	7.6 ± 5.3	6.1 ± 2.6	5.3 ± 1.7	6.6 ± 2.9
Withdrawal to extubation (min)	33.6 ± 12.4	16.5 ± 6.9*	10.3 ± 2.6$^{*,\#}$	12.2 ± 3.0*

Note: Compared with A group, *$p < 0.01$, compared with B group, $^{\#}p < 0.05$.

Table III. SBP, DBP, HR, BIS and 95% SEF changes of the 4 groups during each period of anesthesia.

Index	Group	T_1	T_2	T_3	T_4	T_5	T_6	T_7
SBP (mmHg)	A	121.1 ± 19.0	84.3 ± 18.0$^{\Delta}$	103.7 ± 9.2	78.4 ± 14.4$^{\Delta}$	70.0 ± 11.4$^{\Delta}$	75.7 ± 17.1$^{\Delta}$	108.1 ± 12.2
	B	110.4 ± 17.4	85.7 ± 5.6$^{\Delta}$	111.0 ± 19.1	94.6 ± 14.7$^{\Delta}$	78.7 ± 16.5$^{\Delta}$	95.8 ± 20.8$^{\Delta}$	105.7 ± 19.0
	C	124.0 ± 12.3	87.5 ± 13.5$^{\Delta}$	110.5 ± 20.0	94.0 ± 12.7$^{\Delta}$	93.4 ± 9.2$^{\Delta}$	103.5 ± 12.0$^{\Delta}$	116.4 ± 12.5
	D	118.2 ± 11.5	80.2 ± 13.5$^{\Delta}$	106.2 ± 23.3	90.6 ± 23.1$^{\Delta}$	98.2 ± 19.1$^{\Delta}$	105.2 ± 12.7$^{\Delta}$	119.2 ± 4.6
DBP (mmHg)	A	83.0 ± 22.0	45.1 ± 12.6$^{\Delta}$	60.6 ± 15.1	37.4 ± 12.5$^{\Delta}$	33.6 ± 14.5$^{\Delta}$	44.3 ± 13.7$^{\Delta}$	63.9 ± 16.0
	B	69.9 ± 19.5	41.6 ± 8.9$^{\Delta}$	66.1 ± 17.5	60.0 ± 15.1$^{\Delta}$	42.8 ± 8.3$^{\Delta}$	54.8 ± 24.0$^{\Delta}$	65.0 ± 19.2
	C	70.6 ± .11.6	44.3 ± 10.6	65.9 ± 18.2	63.3 ± 16.7$^{\Delta}$	57.9 ± 9.3$^{\Delta}$	61.6 ± 12.4$^{\Delta}$	75.0 ± 9.6
	D	68.2 ± 10.5	39.8 ± 10.5$^{\Delta}$	58.8 ± 24.4	59.4 ± 25.4$^{\Delta}$	62.8 ± 20.1$^{\Delta}$	69.2 ± 14.8$^{\Delta}$	83.6 ± 10.3
HR (n/min)	A	184 ± 21	150 ± 14$^{\Delta}$	156 ± 14	144 ± 24$^{\Delta}$	128 ± 17$^{\Delta}$	139 ± 16$^{\Delta}$	164 ± 20
	B	153 ± 23	121 ± 16$^{\Delta}$	142 ± 23	122 ± 16$^{\Delta}$	114 ± 11$^{\Delta}$	137 ± 11$^{\Delta}$	142 ± 19
	C	126 ± 25	101 ± 18$^{\Delta}$	112 ± 30	98 ± 19$^{\Delta}$	87 ± 14$^{\Delta}$	106 ± 24$^{\Delta}$	138 ± 19
	D	123 ± 28	100 ± 11$^{\Delta}$	121 ± 13	91 ± 11$^{\Delta}$	84 ± 14$^{\Delta}$	92 ± 17$^{\Delta}$	116 ± 22
BIS	A	95.4 ± 5.9	47.9 ± 9.7$^{\Delta,*}$	45.0 ± 14.1$^{\Delta,*}$	37.4 ± 10.1$^{\Delta,*}$	36.9 ± 7.5$^{\Delta,*}$	47.3 ± 8.9$^{\Delta,*}$	76.1 ± 16.0$^{\#}$
	B	94.8 ± 5.0	56.9 ± 14.0$^{\Delta}$	58.4 ± 13.8$^{\Delta}$	51.4 ± 16.1$^{\Delta}$	58.2 ± 12.6$^{\Delta}$	67.1 ± 15.3$^{\Delta}$	80.8 ± 12.6
	C	96.1 ± 3.4	65.4 ± 9.4$^{\Delta,*}$	70.0 ± 8.7$^{\Delta,*}$	68.0±4.5$^{\Delta,*}$	68.1 ± 7.4$^{\Delta,*}$	74.3 ± 10.0$^{\Delta,*}$	92.0 ± 7.1$^{\#}$
	D	94.4 ± 4.3	46.6 ± 5.9$^{\Delta}$	55.8 ± 7.7$^{\Delta}$	47.4 ± 13.0$^{\Delta}$	49.6 ± 10.8$^{\Delta}$	76.2 ± 10.3$^{\Delta}$	90.6 ± 7.9$^{\#}$
95% SEF	A	20.6 ± 5.3	11.3 ± 4.6$^{\Delta,\&}$	10.1 ± 3.8$^{\Delta,\&}$	9.2 ± 4.3$^{\Delta,\&}$	9.7 ± 3.6$^{\Delta,\&}$	12.5 ± 5.2$^{\Delta,\&}$	18.5 ± 2.6
	B	18.9 ± 8.1	20.4 ± 4.1$^{\&}$	18.7 ± 6.5$^{\&}$	16.9 ± 6.6$^{\&}$	18.1 ± 4.5$^{\&}$	20.5 ± 4.6$^{\&}$	21.5 ± 5.4
	C	22.3 ± 5.6	22.3 ± 2.9$^{\&}$	23.0 ± 3.0$^{\&}$	23.4 ± 2.2$^{\&}$	23.2 ± 2.1$^{\&}$	24.7 ± 1.5$^{\&}$	25.4 ± 4.3
	D	21.8 ± 2.5	18.6 ± 3.0$^{\&}$	20.2 ± 2.6$^{\&}$	18.3 ± 4.4$^{\&}$	18.7 ± 2.9$^{\&}$	26.0 ± 2.0$^{\&}$	22.3 ± 2.2

Note: Compared with T1, $^{\Delta}p < 0.01$; compared with C group, $^{*}p < 0.01$; and C, D group, $^{\#}p < 0.05$; and B, C, D group, $^{\&}p < 0.01$.

waveforms between consciousness and sleep as well as maintain and quantifying the non-linear relationship among the original EEGs to predict sedative and hypnotic levels[9–12]. However, considering that in children, brain development and synapse formation continue until five years of age, young children's EEGs are different from those of older children and adults. Given that the BIS algorithm is based on the integrated analysis of the original EEGs of older children and adults, whether this method can be applied to young children still remains the subject of further study. The results of this study show that under anesthesia with the same dose of propofol and remifentanil, the BIS values of A group were consistently less than those of C group. During awake extubation, the BIS values of A group were significantly less than those of C and D groups, indicating an obvious difference in BIS values between children and adults. The younger the children, the lower the BIS value will be. During loss of consciousness and recovery, the BIS values of small babies were significantly lower than those of children older than two years. This result contradicts those of previous studies. The present study found that BIS possibly reflects propofol sedation in infants and children, as well as relative stability in the airway and hemodynamics[13]. Another study has shown that at the same propofol plasma-effect concentrations, young children exhibit much higher BIS values than adults, and that during consciousness loss and recovery, the BIS values of young children are significantly higher than those of adults[3], indicating a large deviation in using BIS to monitor children. Weber[14] also reported that remifentanil does not affect the BIS of children.

The combination of propofol and remifentanil has been widely used in adults to maintain anesthesia and has gradually been adopted in pediatrics. Remifentanil is a synthetic opioid -receptor agonist with ultrashort effectiveness and could be rapidly degraded by nonspecific esterase in organs and plasma. The elimination half-life of remifentanil is 3 min to 10 min. Regardless of the duration of intravenous infusion, the plasma half-life is always less than 4 min, which is independent of age. The drug clearance rate of remifentanil is approximately 40 $ml \cdot min^{-1} \cdot kg^{-1}$, and its drug distribution and clearance are correlated with age. In two-year-old to 12-year-old children, the metabolism of remifentanil is consistent with that of adults, whereas in newborns and infants, remifentanil is unlike other opioids and has a faster clearance rate[15]. The pharmacokinetic parameters of propofol in children are significantly different from those in adults and also differ among children of various ages. In TCI studies of children with propofol, the results showed that the central chamber volume of children is four times that of adults based on weight and that the clearance significantly increased[16]. This result indicates that to achieve similar plasma concentrations and anesthetic effect, the propofol dose of the initial treatment should be larger in children than in adults, with rapid recovery. In the present study, no statistically significant difference was found among the four groups in terms of spontaneous breathing recovery time. The extubation times of three-month-old children were significantly longer than those of the other age groups. Differences in extubation time were also found between children over two years old and children three months to two years old. Given that remifentanil has a relatively small impact on recovery time, considering that the BIS values of A group were lower than those of C group, the same dose of propofol infused intraoperatively in this experiment might be relatively large for younger children, particularly those under three months old, thereby delaying recovery.

The combined application of propofol and remifentanil causes larger hemodynamic changes. After induction, a drop in blood pressure and heart rate was observed in the four groups. Propofol has a depressant effect on the cardiovascular system. Pessenbacher[17] reported that the initial blood pressure decreases by approximately 10% as a result of early propofol-induced anesthesia in children under three years old, decreases another 10% during the early maintaining-anesthesia period, and then relatively stable arterial pressure is maintained during the maintenance period. By contrast, the blood-brain equilibration time of remifentanil is short. Blood pressure and heart rate decrease 2 min after the injection. During intubation, because of the reflective sympathetic-adrenal system stimulant, blood pressure and heart rate elevate with no significant difference from the pre-induction, indicating that remifentanil could effectively suppress the stress response during intubation. From skin incision to spontaneous breathing recovery, circulation remains in a steady state, indicating that the combination of propofol and remifentanil could provide a relatively stable state of anesthesia when in the anesthesia maintenance stage in different-aged children.

In adults, 95% SEF, like BIS, utilizes EEG information, instantly reflecting the degree of inhibition in the central nervous system by anesthetics as well as the degree of sedation by propofol[18]. In the present study, after anesthesia was induced, only the 95% SEF of the three-month old children decreased significantly, contrary to those of the other three groups. This result indicates that 95% SEF has little connection with sedation in children and would thus be a less accurate basis for the assessment of sedation than BIS.

Certain correlations have been reported among adult hypotension[4], deep anesthesia (BIS < 45)[5,6], and postoperative recovery and mortality, indicating that continuous monitoring of blood pressure and BIS during anesthesia helps predict postoperative mortality. Similar studies have not been conducted on pediatric patients. Some scholars have found that BIS shows a linear correlation with pediatric anesthetics[19]. However, whether using BIS to guide the implementation of anesthesia in children would reduce the use of narcotics, shorten extubation time, prevent excessive sedation, and affect the turnover of children needs further investigation.

In this experiment, the same dose of propofol and remifentanil was administered. The BIS values of A group at different time points after induction were lower than those of C group. The recovery time of A group was also prolonged, suggesting a possible overly large continuous infusion dose for small babies. Therefore, the infusion rate could be reduced to improve postoperative recovery and reduce the application of anesthesia.

During surgery under anesthesia, the patient should be kept in a state of unconsciousness so as not to perceive or remember the harm caused by surgical stimulation. A balance is kept between anesthetic inhibition of the central nervous system and awakening caused by noxious stimuli[20,21]. Studies have shown that BIS and 95% SEF could fully integrate in adults and use the information provided by brain waves, instantly reflecting the degree of inhibition and changes in consciousness enacted by the anesthetic on the central nervous system. In this study, the BIS values of the four groups at different time points after induction decreased significantly compared with those during pre-induction. However, no significant differences were found in BIS values during intubation, post-induction, skin incision, withdrawal, and spontaneous breathing recovery. Hemodynamic parameters, similar to blood pressure and heart rate, also decreased significantly before and after induction ($p < 0.01$), consistent with variations in BIS value. Although blood pressure and heart rate during intubation were not statistically significant compared with those during pre-induction, values of these parameters also increased, indicating that the central nervous systems of the four groups were significantly suppressed after the induction of anesthesia, resulting in significantly lower BIS values. For the stress response caused by intubation, the hemodynamics changed, contrary to the BIS values, indicating that BIS does not monitor well the autonomic responses caused by noxious stimuli. Thus, intraoperative anesthetic depth should be monitored using the two methods simultaneously.

Conclusions

The combined application of propofol and remifentanil in anesthesia is safe and effective for different-aged children. The BIS values of children over three months old are similar to those of adults. The BIS values are lower in infants under three months old, with prolonged recovery time, indicating that the infusion rate should be reduced appropriately for the maintenance of anesthesia with propofol.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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