THE BISPECTRAL INDEX SYSTEM IN PEDIATRICS - IS IT RELATED TO THE END-TIDAL CONCENTRATION OF INHALATION ANESTHETICS? -

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Abstract

Background and Goal of study: Bispectral Index (BIS) has been used in adults to measure depth of anesthesia using various protocols. Though less investigated in children, there is growing evidence that bispectral index seems adequately calibrated for monitoring the depth of isoflurane and sevoflurane anesthesia in pediatric patients.

A range of BIS scores (40-60) has been seen to be an indicator for an acceptable level of hypnosis and anesthesia. Davidson and Czarnecki have reported that, at an end-tidal concentration of 1 MAC, the BIS for halothane was significantly greater than isoflurane (56.5 ± 8.1 vs. 35.9 ± 8.5). The explanation given is the fact that the volume concentration of the MAC value is inversely related to the BIS value. Accordingly, it is expected that the BIS value at 1 MAC of desflurane must be less than halothane and isoflurane.

Materials and Methods

This is a clinical cross-over, prospective, randomized double blinded study. 90 pediatric patients scheduled for below umbilical surgery, under

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general and caudal analgesia, were allocated into 4 study groups. The BIS values at a relatively equipotent doses of the previously mentioned agents were compared with each other in the same group and between other groups.

Results: At a relatively equipotent doses, the mean BIS value for halothane {60.4 ± 5.6} was significantly higher than isoflurane {45.5 ± 9.2} and desflurane {38.5 ± 9.2} $P<0.001$). Equivalent end-tidal doses of different inhalational anesthetics do not necessarily have the same effects on cortical and sub-cortical functions and consequently on EEG.

Conclusion: The use of a relatively equipotent end-tidal concentration of different inhalational agents may result in different BIS values.

Key Words: **B**ispectral analysis. **P**ediatric anesthesia; halothane; desflurane; isoflurane; electroencephalography.

Introduction

Among the earliest systematic observations of the physiologic effects of anesthetic agents were that of John Snow's and Guedel's descriptions of the various stages of ether anesthesia. While the aim of these descriptions was initially to avoid hazards of overdose, nowadays, it is equally important to avoid "under dosage". The bispectral index (BIS) is a continuous processed electroencephalography parameter that has been developed to measure the hypnotic component of some anesthetic agents.

The BIS has been assessed in adult patients receiving propofol, midazolam, fentanyl, isoflurane and sevoflurane[1-6] and in children7. Although less investigated in children, yet there is growing evidence that bispectral index seems adequately calibrated for monitoring the depth of isoflurane and sevoflurane anesthesia in pediatric patients[8-9]. The BIS values in children undergoing routine general anesthesia with a variety of IV and inhaled anesthetics were reported to be comparable to those reported in adult controls[10].

Awareness is an out of sight problem in the pediatric population. Its incidence is not easily identifiable because of a young child's reduced capacity to report events and the difficulty of differentiating conversation heard during emergence or in the PACU, from those heard during anesthesia. For these reasons, a reliable monitor of depth of anesthesia may be equally or even more important in pediatrics than in adult populations.

This prospective study was designed to evaluate the correlation between BIS and the end-tidal concentration of different inhalational agents in pediatric patients undergoing below umbilical surgery under general anesthesia and caudal analgesia. We assessed and compared the BIS *(BIS, Aspect Medical Systems, Natick, MA)* value in patients receiving halothane (0.9%), isoflurane (1.3% or 1.6%) or desflurane (6%) in O_2/air mixture.

Methods and Materials

Approval of the study design was obtained from the hospital ethics committee. After written informed consent from parents, 80 pediatric patients (2-12 years old), ASA classification I-II, scheduled for elective below umbilical surgery, expected to last more than 45 minutes (hypospadius repair or orchidopexy), were randomly assigned to one of four study groups of equal numbers (n = 20) according to a computer-generated random numbers table.

The study design was explained to the parents in the preoperative interview. Children were excluded from the study if preoperative sedation was mandatory. Other exclusion criteria were: mental diseases, epilepsy, history of developmental delay, children on any medications affecting the CNS, or contraindication to inhalational anesthetics, and/or failed or improperly working caudal analgesia as reflected by increase of heart rate or blood pressure by more than 20% of basal level with skin incision. Other possible confounding factors such as varying carbon dioxide, temperature changes were controlled and kept constant over physiological ranges, in all children.

The mother was allowed to accompany the child if separation at receiving area was difficult. On arrival in the operating room, in addition to routine monitoring heart rate (HR), non-invasive arterial pressure (NIBP) and pulse oximetry (SpO2), the EEG signal was acquired using pediatric BIS sensor *(Aspect Medical System, Newton, MA)* placed on child's forehead according to the manufacturer's instructions and was connected to a BIS monitor {A-2000 monitor with version 3.21 software *(BIS, Aspect Medical Systems, Newton, MA)*}.

Baseline values for BIS and hemodynamic variables were obtained. All children then breathed through a face mask connected to a semiclosed anesthetic circuit. The concentrations of carbon dioxide, inhalational agents and oxygen were measured continuously using an infrared anesthetic gas analyzer.

Anesthesia was induced with propofol (2mg/kg) or sevoflurane inhalation (as appropriate). Rocuronium in a dose of 0.6mg/kg was given for endotracheal intubation and mechanical ventilation. After induction of anesthesia, the child was positioned for caudal analgesia, 1ml/kg of bupivacaine 0.25% with maximal volume 25ml.

Anesthesia was maintained by one of the three studied inhalational agents in O_2/air mixture of 3L/min. The groups were named according to the sequence of use of two of the three studied inhalational anesthetics, namely halothane, isoflurane and/or desflurane. The HI group had halothane then isoflurane. The IH group had isoflurane then halothane. The HD group had halothane then desflurane. The DH group had desflurane then halothane. All agents were given in an oxygen/air mixture without nitrous oxide, and no opioids were used (neither in caudal nor IV).

The first agent was started soon after endotracheal intubation and continued for at least 15 minutes aiming for enough time for the decreasing effect of propofol or wash out of sevoflurane. At intended end-tidal concentration of 1 MAC of the first agent, the BIS reading (on the monitor which was rotated to the back of the anesthesia machine) was taken by an anesthesia technician who was blind to the anesthetic agents in use (the anesthetist was blind to all BIS value readings). The BIS reading was taken as the average of 4 readings 15 seconds apart (over 1 minute interval) with smoothing ratio set at 15 seconds. The first agent was then truned off and the second agent was ongoing gradually increasing concentration for another smoothing time of 15 minutes. When disappearance of the first agent and an intended end-tidal concentration of the second agent of 1 MAC was reached, the anesthethist asked the technician to record the BIS value as mentioned before.

MAC for halothane was taken as 0.9 vol%, 1 MAC for isoflurane was taken as 1.3 vol% for children older than 5 yr and 1.6 vol% for those between 2 and 5 yr old, 1 MAC for desflurane was taken as 6 vol%. We choose 6 vol% for desflurane which is about 25% below 1 MAC in this age group (8.2-8.7)[11] because we are using desflurane in every day practice in a dose around this figure in the same studied clinical settings with acceptable BIS values. So we found that it is unethical to expose patients to unnecessary higher doses.

The BIS values at end-tidal concentration of 1 MAC of different agents in the same group were compared using paired-samples t-test. The BIS values at end-tidal concentration of 1 MAC of the same agent in different groups were compared using independent t-test or One way Analysis Of Variance (ANOVA) as appropriate, and Bonferroni test was performed for post hoc comparisons within and between groups assuming equality of variances. Other continuous variables were analyzed using ANOVA and nonparametric variables were analyzed using the chi-sequare test as appropriate. Data are expressed as mean values ± SD unless otherwise stated. Differences were considered statistically significant for $P<0.05$.

Results

Demographic data of the child’s age, weight and sex were comparable in all study groups. Because of the high proportion of hypospadius and orchidopexy procedures, male patients predominated but the gender distribution was not significant difference in the induction technique in term of propofol/sevoflurane ratio (p = 0.9) (Table 1).

Table 1

Details of patients and anesthesia

	HI group	IH group	HD group	DH group	P value
Age-months (media-range)	41.0 (24-132)	33.0 (24-100)	38.0 (24-120)	30.0 (24-135)	.87
Weight-kg (mean-SD)	20.5 (5.3)	17.0 (3.0)	19.9 (5.6)	18.9 (5.0)	0.17
Sex-ratio (male/female)	18/2	16/4	14/6	17/3	0.41
Induction technique (propofol/ sevoflurane ratio)	12/8	11/9	13/7	11/9	0.9

Table 2 shows the BIS values (mean ± SD) at end-tidal concentration of 1 MAC of halothane, isoflurane and desflurane in the HI, IH, HD and DH groups.

Table 2

BIS values (mean±SD) at 1 MAC of halothane, isoflurane and desflurane in the HI, IH, HD and DH groups.

Agent	HI	IH	HD	DH
Halothane	62.8 (7.9)	61.0 (5.2)	59.0 (3.3)	58.8 (4.3)
Isoflurane	46.3 (9.3)	44.7 (9.2)	---	---
Desflurane	---	---	39.3 (10.3)	37.7 (8.1)

Data are expressed as mean (SD)

Table 3 shows the mean and 95% CI of the difference between different agents in the same group (paired t-test). There was no statistically significant difference between BIS values at end-tidal concentration of 1 MAC of same agent in different groups that excludes a carry over effect.

Table 3
Mean and 95% CI of the difference between different agents in the same group (paired t-test).

	Mean (SE)	95% Confidence Interval of the Difference	P value
Difference between *H1 – I1*	16.5 (9.4)	12.1 - 20.9	<0.001
Difference between *H2 – I2*	16.4 (8.9)	12.2 – 20.5	<0.001
Difference between *H3 – D3*	19.7 (11.0)	14.5 – 24.9	<0.001
Difference between *H4 – D4*	21.2 (9.5)	16.7 – 25.6	<0.001

H1 = halothane in HI group, H2 = halothane in IH group, I1 = isoflurane in HI group, I2 isoflurane in IH group, D3 = desflurane in HD group and D4 = desflurane in DH group.

Analysis of data of the whole 80 children showed that there was statistically significant difference between the BIS value at 1 MAC halothane and 1 MAC of either isoflurane or desflurane (Table 4). ANOVA test showed that there is statistically significant difference (p<0.001), Bonferroni test for post hoc multiple comparisons showed that the difference is significant between halothane and isoflurane, halothane and desflurane and isoflurane and desflurane (p<0.001).

Table 4
Descriptive statistics of 1 MAC of halothane, isoflurane and desflurane in all study groups (normally distributed data).

	Number of patients	Mean BIS value	Std. Deviation	Minimum	Maximum	95% Confidence Interval for Mean	
halothane	80	60.4	5.9	44.0	69.0	59.1	61.6
isoflurane	40	45.5	9.2	31.0	69.0	42.5	48.4
desflurane	40	38.5	9.2	28.0	63.0	35.5	41.4

Discussion

The ability of general anesthetics to suppress somato-motor responses to surgical incision and other noxious stimuli is of particular clinical relevance for evaluation of adequacy of anesthesia. When the blockade is due to inhaled agents, this effect can be quantified as the minimum alveolar concentration (MAC), which measure only one component of the triad of anesthesia (unconsciousness and lack of recall, analgesia and immobility).

Instead, analysis of EEG was used for evaluation of depth of anesthesia. Newer sophisticated computerized technology designed for analysis of the EEG activity proved to be superior indicators of anesthetic depth, and titration of anesthetic drugs with ensuing advantage of improved recovery and reduction in frequency of awareness. These newly introduced monitors for depth of anesthesia depending on computerized analysis of filtered and/or repaired EEG waveforms include BIS and Entropy[12].

There are few studies evaluating the BIS in pediatric populations. Simon et al[8] investigated the concentration-response relationship between the BIS and the end-tidal isoflurane concentration. Davidson and Czarencki[7] compared the BIS values at equipotent doses (1 MAC) of halothane and isoflurane. They concluded that BIS values at 1 MAC of halothane is significantly higher than that at equipotent dose of isoflurane.

Our findings are comparable with that of Davidson and Czarencki as regard the BIS difference between halothane and isoflurane (mean difference 14.9-95% CI 11.4 to 18.5). In addition, however, our findings show that the difference is much more significant between halothane and desflurane (mean difference 21.9-95% CI 8.4 to 25.4). The previous results are contradictory to the assumed character of BIS which is a pharmacodynamic end-point, i.e., as a measure of hypnosis, should be independent on the hypnotic used, as has been demonstrated in adults[2].

Our results show clearly that the mean difference of BIS values between equipotent doses of halothane and desflurane is more than that between halothane and isoflurane. However, we can not justify from these findings that there is an inverse relationship between the MAC and the BIS values. That is because we actually studied correlation of BIS value with a non-steady end-tidal concentration of inhalational agents and not the alveolar concentration (the 'A' in MAC stands for alveolar). Our results reflect the effect of different pharmacokinetic properties of the three anesthetics, with the slowest-and therefore most incomplete-cerebral uptake for halothane, and the fastest for desflurane, with isoflurane in between. As a consequence BIS values for desflurane were significantly lower than for isoflurane and halothane, and BIS for isoflurane was lower than for halothane. Lu et al[13] have shown that for desflurane, it takes about 24 minutes, for isoflurane it takes 50 minutes and for sevoflurane it takes 40 minutes until uptake into the brain is complete. Further studies are needed to correlate BIS with steady-state alveolar concentration of different inhalational agents to validate MAC as a measure of hypnotic component of general anesthesia.

One of the limitations to this study is the confounding factor the surgical stimulus, taking into consideration that all children received caudal analgesia done by a single investigator and that exclusion criteria included a manifestation of improper analgesia.

In summary, the use of a relatively equipotent end-tidal concentration of different inhalational agents may results in different BIS values.

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