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Original Article

The performance of Bispectral Index in children during equi-MAC halothane vs. sevoflurane anaesthesia

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Summary

Background and objective: The reliability of the Bispectral Index for evaluating and monitoring the depth of general anaesthesia in children is not as great as for that in adults. Therefore we analysed Bispectral Index performance in children by comparing changes in Bispectral Index values during a standardized and equipotent anaesthetic regimen using either halothane or sevoflurane for the induction and maintenance of general anaesthesia. Special interest was focussed on excitation during induction, and whether it was associated with simultaneous changes in Bispectral Index scores. *Methods:* Twenty children (3–15 yr, ASA I–II) scheduled for general surgery were randomly allocated to either halothane (10 patients) or sevoflurane group (10 patients). Anaesthesia was induced by 3% halothane or 7% sevoflurane, either agent administered with 50% N_2O in oxygen for 5 min, the period from the beginning of induction until intubation. Thereafter, anaesthesia was maintained by the respective volatile agent at 1 MAC (minimum alveolar concentration; in addition to 70% N_2O in oxygen) and supplemented with remifentanil infusion adjusted to maintain the heart rate and mean arterial pressure to within 20% of the baseline values. Excitation at induction was defined as involuntary muscular movements. *Results:* Sevoflurane induction produced a more rapid depression in Bispectral Index than halothane, the mean difference being greatest (47 Bispectral Index score) at 105 s. Excitation occurred in three patients during sevoflurane induction, which coincided with increases in Bispectral Index values in two of the three patients. During the maintenance phase at 1 MAC, the Bispectral Index (mean ± SD) was 57±7 for halothane and 47±9 for sevoflurane ($P < 0.05$). The remifentanil doses did not differ between both groups. *Conclusion:* In children, halothane anaesthesia was associated with higher Bispectral Index values than sevoflurane when administered at 1 MAC. Large individual variation in Bispectral Index occurred within both groups. Due to these limitations, one should be cautious when interpreting paediatric Bispectral Index data.

Keywords: ANAESTHESIA INHALATIONAL; CHILD; CHILD PRESCHOOL; HALOTHANE; SEVOFLURANE; BISPECTRAL INDEX.

Introduction

Although the benefits of Bispectral Index (BIS) monitoring as a measure of depth of anaesthesia are obvious for adults, this is not necessarily the case for children. After some initially promising findings [1], the reliability of BIS, as a tool to indicate the depth of inhalational anaesthesia for children under school age and especially for infants, has been questioned [2–7].

During the past decade, sevoflurane has replaced halothane as the gold standard in paediatric anaesthesia [8]. However, halothane is still used to some extent, not only for reasons of economy but also

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for its well-established clinical advantages. Both remain excellent agents for face-mask induction.

Consequently, it would be useful in paediatric practice to be able to measure reliably the depth of anaesthesia during both its induction and maintenance phases. For every child, the level of anaesthesia must be titrated as appropriate for the surgical stimulation. First, this is done by excluding the underdose of anaesthetics such that awareness during anaesthesia is unlikely. Second, excluding the anaesthetic overdose, which will decrease the side-effects such as slow recovery and postoperative nausea and vomiting. Data in the Pediatric Perioperative Cardiac Arrest Registry [9] indicate that halothane is responsible for two-thirds of all medically related cardiac arrests. The majority of these dose-related cardiac arrests occurred during induction with unintended high doses of halothane causing cardiac depression.

There are no earlier studies published that compare the performance of BIS during induction with halothane with that of sevoflurane in children. As yet, only the effects of sevoflurane induction on BIS have been reported [10]. Excitation (agitation) during induction with either halothane or sevoflurane is a well-known phenomenon in paediatric anaesthesia [10–12]. Moreover, excitation is common, especially when sevoflurane is used without N_2O [11,12]. Constant and colleagues [12] reported a high incidence of excitation during induction with either agent, but this was not associated with clinical or electrical seizure activity. Moreover, these authors reported that the electroencephalogram (EEG) profiles of patients given either sevoflurane or halothane were distinctly different from each other. Several case reports reported seizure-like movements in children undergoing sevoflurane face-mask induction [13,14].

The aim of the present study was to compare the changes in BIS values between equipotent sevoflurane and halothane regimes throughout induction and 30 min of the maintenance phase of general anaesthesia. Special interest was focussed on the clinical signs of the excitation phenomenon during induction of either high-dose halothane or sevoflurane, and whether such excitation was associated with simultaneous changes in BIS values.

Methods

After obtaining the Ethics Committee's approval (Hospital for Children and Adolescents, Helsinki University, Helsinki, Finland) and also after obtaining written informed consent of the patients' parents, 20 children were studied. They were randomly allocated to either halothane (10 patients) or sevoflurane group (10 patients). The inclusion criteria were: ASA class I–II, age between 3 and 15 yr, and an elective orthopaedic or urological operation with an estimated duration of between 0.5 and 3 h under general anaesthesia without regional anaesthesia. Children were excluded if they had a history of disease or medication affecting the central nervous system or if the surgery affected the head or the neck of the child.

All included patients received a standardized anaesthesia without premedication. Patients underwent face-mask induction with either 3% halothane or 7% sevoflurane, each in a mixture of 50% N_2O in oxygen, and administered via a tight-fitting face mask for a period of 5 min. When the spontaneous breathing diminished, the patients were manually ventilated to avoid hypoventilation. The patients were intubated promptly at 5 min from the beginning of induction. After intubation all patients were ventilated with a mixture of 70% N_2O in oxygen and the respective volatile agent adjusted to end-tidal concentration of 1 MAC (minimum alveolar concentration) throughout the maintenance of anaesthesia as described in the studies by Gregory and colleagues [15] and Lerman and colleagues [16]. Therefore, the end-tidal concentrations were 0.8% for halothane and 2.5% for sevoflurane. During the controlled ventilation, end-tidal CO_2 was maintained at 35–40 mmHg (ADU S/5 and S/5 Anaesthesia Monitor; Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). In addition, anaesthesia was supplemented with a continuous infusion of remifentanil at 0.05–1 $\mu g\,kg^{-1}\,min^{-1}$. The initial dose was 0.05 $\mu g\,kg^{-1}\,min^{-1}$, which was appropriately adjusted to maintain the heart rate (HR) and mean arterial pressure to within 20% of the baseline values as obtained before the induction of anaesthesia. Neuromuscular blocking agents were not administered. The attending anaesthesiologist controlled the anaesthesia, titrated the remifentanil dose according to protocol and kept the end-tidal anaesthetic constantly at 1 MAC. At the end of surgery, intravenous (i.v.) paracetamol at 15 $mg\,kg^{-1}$ and ketoprofen at 1 $mg\,kg^{-1}$ were administered to all patients for the preventive treatment of postoperative pain. After the operation was completed volatile agents and remifentanil were discontinued without any tapering. The patient was extubated when sufficient spontaneous breathing returned, then transferred to the post-anaesthesia care unit (PACU). For postoperative pain, morphine 0.1 $mg\,kg^{-1}$ i.v. was also given when needed.

The anaesthesiologist (TT) was blinded to BIS monitoring for all the patients throughout the study period. Before the anaesthetic induction, a disposable adult BIS Sensor (Aspect Medical Systems, Newton, MA, USA) was attached to the forehead

according to the manufacturer's instructions. Electrode impedance was considered acceptable if it remained below 7.5 kΩ. Impedance was checked at the start and the end of the recording. It was also checked whenever unreliable tracking of the EEG signal was suspected. Corrective actions were immediately made, if the acceptable impedance level was exceeded. The EEG sampling rate for the BIS (BIS XP, version 3.2; Aspect Medical Systems, Newton, MA, USA) was 256 Hz; the smoothing window was 15 s. BIS indices together with all other measured parameters were collected by and stored in a laptop computer using the S/5 Collect software (Datex-Ohmeda Division, Instrumentarium Corp.) for further off-line analysis. BIS recording was started in the operating room prior to induction in order to obtain the baseline values and continued until the respective patient was awake in the PACU.

The anaesthetic maintenance doses of halothane and sevoflurane were different to those of the 5-min induction period. The analyses of the BIS data samples were divided into two periods: (1) the induction period: from the beginning of the anaesthetic induction phase up to its end 5 min later at which time intubation was performed) and (2) the maintenance period: 30 min of recordings, starting at 5 min after intubation. In addition, end-tidal halothane, sevoflurane, N_2O and CO_2 concentrations, electrocardiogram, HR, non-invasive blood pressure (measured at 5-min intervals), pulse oximetry saturation, temperature (S/5 Anaesthesia Monitor) and the time to loss of eyelash reflex were monitored during anaesthesia.

Signs of excitation during the induction period were observed. The criterion of excitation was met, if there were any involuntary muscular movements of the extremities before intubation (up to 5 min after commencing induction). The times of the beginning of and also the duration of excitation were recorded. Other signs of possible excitation were recorded (changes in HR, respiratory rate). The intubation conditions were evaluated according to a paediatric scale [17]. Awareness during anaesthesia was studied using the modified scale by Brice and co-workers [18] performed on three occasions (PACU, on first postoperative day, and by a letter 1 week after the surgery).

Statistical analysis

For the induction analysis, the BIS value recordings during the 5-min period from commencement of induction to immediately before intubation were used. Individual and mean BIS values over time were analysed. The time at which the biggest difference in BIS value between sevoflurane and halothane occurred was determined by subtracting the average BIS values of the agents. Moreover, the minimum of each BIS curve during induction was recorded and the respective time point determined. An unpaired *t*-test was used to test the differences between the time points for halothane and sevoflurane BIS minima. For maintenance phase analysis, data were analysed over a 30-min period, which commenced 5 min after the maintenance phase began (5 min after intubation). The assumption of presence of a normal distribution of the data was verified with the Kolmogorov–Smirnov test and Q–Q plots. The intraoperative BIS values between the agents at 1 MAC were analysed by the unpaired *t*-test. Statistical analyses were performed using a SPSS V14.0 (SPSS Inc, Chicago, IL, USA), all other data processing and analyses were done using Matlab V7.3 (The Mathworks Inc, Natick, MA, USA). A *P*-value less than 0.05 was considered statistically significant. Based on our pilot and a previous study [19] the mean difference of BIS between sevoflurane and halothane during maintenance was estimated to be 17 units with a SD of 10 units. To detect such a difference between means with a power of 0.95 and α, at a significance level of 0.05, 10 patients in each group were calculated to be sufficient. Values are expressed as mean ± SD unless otherwise stated.

Results

Twenty patients were enrolled into the study, and no patients were excluded. Table 1 summarizes the patients' data for each group. Sevoflurane induction produced a more rapid depression in BIS values compared to halothane. The greatest difference in BIS values of 47 ± 25 was recorded at 105 s from the beginning of induction (Fig. 1). The lowest BIS values during the induction phase were measured at 279 and 146 s in halothane and sevoflurane groups, respectively ($P < 0.005$). The mean ± SD (range) BIS values at the start of intubation were 31 ± 19 (20–65) and 37 ± 15 (21–65) for halothane and sevoflurane groups, respectively (NS). The intubation conditions were good or excellent (score 1–2) for both groups (NS).

During the maintenance phase at 1 MAC, the mean ± SD (range) BIS was 57 ± 7 (46–66) for halothane and 47 ± 9 (33–64) for sevoflurane ($P < 0.05$). Box plots showing the distribution of all BIS observations during maintenance are shown in Figure 2. The mean ± SD remifentanil doses were 0.23 ± 0.08 and 0.2 ± 0.1 $\mu g\,kg^{-1}\,min^{-1}$, for halothane and sevoflurane groups, respectively (NS). Awareness was not detected in the postoperative questionnaire.

Table 1. Patient characteristics.

	Halothane group ($n = 10$)	Sevoflurane group ($n = 10$)
Age (yr)	9.5 ± 3.5 (3.0–15.8)	9.4 ± 3.0 (4.1–14.8)
Weight (kg)	34.8 ± 17.5 (11.5–62.0)	35.6 ± 14.0 (17.7–59.0)
Sex (M/F)	6/4	4/6
Procedure		
Orthopaedic	7	6
Urological	3	4

Data are presented as number of patients or mean ± SD (range).

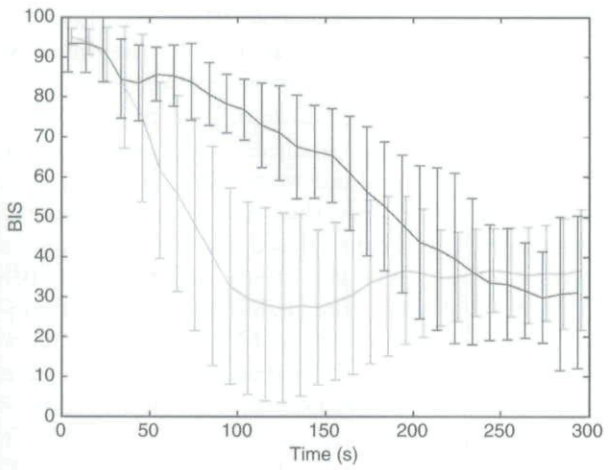

Figure 1.
The Bispectral Index values (mean ± SD) during the induction period of 5-min in the halothane (black) and sevoflurane (grey) groups.

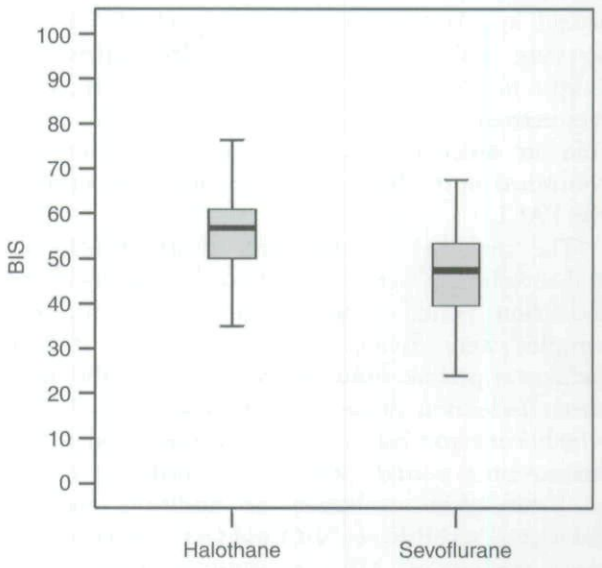

Figure 2.
Boxplot analysis shows the Bispectral Index during the maintenance phase at 1 MAC of halothane or sevoflurane. The boxplots-and-whiskers denote the values of BIS. The bold black line within each box indicates the median; the bottom and the top of the box indicate 25% and 75% range of the group, and the distance between the top and the bottom being the interquartile range. The whiskers indicate the range of variation of data for the group.

The clinical criteria for excitation were met in three out of the 10 patients receiving sevoflurane. None of the patients of the halothane group manifested any excitation. Excitation occurred in three patients during the sevoflurane induction phase, which paradoxically coincided with an increase in the BIS values for two of the affected patients. The characteristics of patients with excitation are shown in Table 2. The excitation periods of the individual BIS curves of the three patients are shown in Figure 3. The excitation ended spontaneously within 90 s in all three patients.

Table 2. Characteristics of excitation in three patients (A, B and C) receiving sevoflurane for induction of anaesthesia.

Patient	A	B	C
Age (yr)	7	4	7
Gender (M/F)	M	F	F
Time to loss of eyelash reflex (s)	55	50	60
Time from the start of induction (s)	120	80	70
Duration of excitation (s)	60	75	75

All three patients also showed increased heart rate and respiratory rate during the excitation.

Discussion

The present study shows that sevoflurane administered at equipotent concentrations produced significantly more rapid depression of BIS values than halothane during induction. This finding has not been reported in children earlier. With halothane there was a progressive decrease in BIS values up to the time of intubation (Fig. 1). The sevoflurane induction was associated with the lowest BIS values at only two and half minutes after induction commenced, in spite of the continuously increasing concentration of sevoflurane in the brain. On the basis of this study, it can be only speculated as to what is the reason for increasing BIS values during sevoflurane induction seen in two out of the three

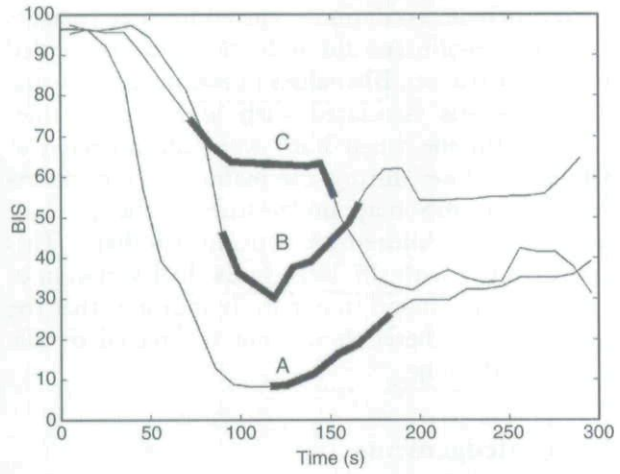

Figure 3.
The individual Bispectral Index curves of the three patients (A, B and C) with excitation during the 5-min period of face-mask induction with 7% sevoflurane (in 50% N_2O in oxygen). The occurrence of excitation has been marked as bolded part of the curve. The criterion for excitation was involuntary muscular movements of the extremities before intubation at 5-min.

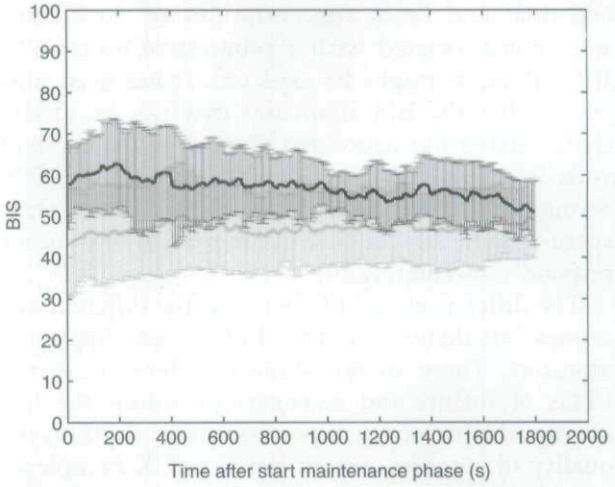

Figure 4.
The Bispectral Index values (mean ± SD) during the maintenance period of 30-min in the halothane (black) and sevoflurane (grey) groups.

patients who had excitation. However, this study may indicate that BIS is not sensitive or reliable enough to show an adequate response to sevoflurane induction at a high dose (7%) maintained for 5 min. A deep level of inhalation anaesthesia must have been reached, as the intubation conditions were good or excellent for both groups (Table 2).

The present study corroborates the previous findings that during the maintenance of anaesthesia significantly higher mean BIS values are observed for halothane than for sevoflurane [19]. Surprisingly, our stable maintenance administered at 1 MAC of halothane or sevoflurane was associated with huge individual variation in mean BIS values (46–66 for halothane and 33–64 for sevoflurane; Fig. 2). The reason for this very high inter-individual variation remains unclear. The age of the child may be the most obvious reason. High BIS values have been found in children under school age [5,6]. However, our patient population was not sufficient enough to allow a meaningful statistical analysis between the child's age and its corresponding mean maintenance BIS value. This finding on the limitations and reliability may be useful for a clinician to exercise caution about interpreting BIS values for monitoring anaesthesia in children. Clinically, the interaction between the potential effects of stimulation due to surgery against inhibition due to opioids on the electrical activity of the cortex and BIS are interesting. However, in the present study a significant part of the BIS sampling was performed before the surgery started. Consequently, Figure 4 shows that under the protocol of our study there were no obvious changes in BIS in respect to surgical stimulation. This must be due to the fact that the doses of the volatile agents were fixed. Moreover, the remifentanil doses were only moderate and showed very little variation between the patients.

Controversy exists regarding the suitability of BIS to measure accurately and precisely the depth of hypnosis in paediatric patients. The validity of BIS for older children is quite clear and has been demonstrated [1,3]. In contrast, the performance of BIS in younger children and, especially in infants is questionable at the present time [2–7]. Age itself seems to affect BIS indices inversely, i.e. the younger the child, the higher the BIS value for a specific MAC-level [5,6]. Davidson and colleagues [3] evaluated the effect of three different end-tidal concentrations of sevoflurane (1.5%, 2.0% or 2.5%) on BIS in children undergoing cardiac catheterization. The change in BIS with increasing sevoflurane concentration was less definite in younger children and infants. Kim and colleagues [5] had similar findings when sevoflurane was administered at three different end-tidal doses (2.0%, 3.0% and 4.0%) to children. The BIS values decreased when end-tidal sevoflurane concentration increased from 2.0% to 3.0%, but paradoxically BIS increased when end-tidal sevoflurane concentration was increased from 3.0% to 4.0%. These curious findings of elevated BIS values associated with deepening sevoflurane steady-state anaesthesia are thus well documented [3,5]. However, associations between BIS values and halothane anaesthesia have never been studied. Our sevoflurane induction data (at non-steady state) seem to support these findings as the increasing

end-tidal and brain concentrations of sevoflurane were not associated with a progressive decrease in BIS values, as might be expected. It has been suggested that the BIS algorithm may not be ideally characterized and structured to measure the depth of volatile anaesthesia in children [8]. This is probably because different anaesthetic agents have their agent-specific effects on EEG to which BIS do not respond to accurately [8].

The differences in EEG between the different age groups challenge all the EEG-based hypnosis-monitors. There are well-known differences in the EEGs of infants and teenagers including the following: the frequency of posterior basic rhythm, the quality of spindles, vertex waves and K complexes in addition to the changes of EEG during drowsiness [20]. In the present study, the children were aged between 3 and 15 yr, and the randomization resulted in similar age distributions within both groups. Therefore, our results should not be biased by the effect of age on EEGs.

Substantially greater BIS values have been recorded for halothane than for sevoflurane, isoflurane and desflurane for maintenance of anaesthesia in children [19,21,22]. The present study's data are in line with the study by Edwards and colleagues [19], who observed that during the maintenance of anaesthesia, significantly higher mean BIS values were obtained for halothane than for sevoflurane. However, in that same study, halothane and sevoflurane (without N_2O) were administered by titrating the dose as appropriate for surgical stimulation, which resulted in non-equipotent end-tidal concentrations of halothane (1.1%) and sevoflurane (2.1%). In our study, we used fixed 1 MAC anaesthetic end-tidal concentrations; this difference in methodology limits the extent to which we can compare our data with those of Edwards and colleagues [19].

We found excitation with clinical signs in three out of 10 patients during sevoflurane induction compared to none in the group receiving halothane (Fig. 3). In two of those patients, a paradoxical increase in BIS values was seen during excitation. The raw EEGs were not recorded, as the aim was to conduct a clinical study applying routine anaesthetic setting and monitoring. Constant and colleagues [10] evaluated the effect of midazolam vs. clonidine premedication on clinical excitation, EEG and BIS during high-dose (8%) sevoflurane induction in children. Interestingly, these authors observed that paradoxical increases in BIS values were preceded by excitation in their patients, whereas in our study we observed that excitation and increase in BIS seemed to coincide with each other. These findings indicate that BIS may not follow the depth of anaesthesia during sevoflurane induction.

To conclude, excitation occurred in three patients receiving sevoflurane for induction that coincided with an increase in BIS values in two of the patients. Halothane was associated with higher BIS values than sevoflurane when both were administered at equipotent doses during the maintenance of anaesthesia. The BIS may underestimate the level of anaesthesia in children when using halothane. This fact, together with the large individual variation of BIS at 1 MAC, found in our study indicates that the depth of anaesthesia should not be steered on the basis of BIS alone.

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