Correlation of bispectral index with end-tidal sevoflurane concentration and age in infants and children

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Background. The bispectral index (BIS) has been evaluated as a tool for measuring depth of anaesthesia, but the use of BIS in a paediatric population is still controversial. This study was designed to evaluate the correlation of BIS with end-tidal sevoflurane concentration and age in infants and children.

Methods. Eighty-one patients undergoing elective urology surgery were allocated into three age groups; 6 months to 2 yr (n = 28), 3–7 yr (n = 33), and 8–12 yr (n = 20). Sevoflurane was administered to achieve steady-state end-tidal sevoflurane concentrations (ETsevo) of 2.0, 3.0, and 4.0%; these were achieved consecutively either from the lowest or from the highest concentration. The BIS (version XP) was monitored continuously.

Results. In all three groups, BIS decreased significantly when ETsevo increased from 2.0 to 3.0% but there was a paradoxical increase in BIS values when ETsevo increased from 3.0 to 4.0%. The non-linear regression analysis showed a significant correlation between BIS and age at each ETsevo. The younger patients showed the higher BIS values.

Conclusions. In children aged 6 months to 12 yr, the BIS increased paradoxically as ETsevo increased from 3.0 to 4.0%. BIS values showed a wide variation in the same ETsevo and the age itself was considered to be a factor affecting the BIS values.


Keywords: anaesthetics volatile, sevoflurane; children; monitoring, bispectral index

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The bispectral index (BIS) was developed by recording EEG data from healthy adults, who underwent repeated transitions between consciousness and unconsciousness, using several different anaesthetic regimens. Like other organ systems, the nervous system is functionally immature at birth, myelination is rapid during the first 2 yr and completed by 7 yr of age.¹ Therefore, the BIS algorithm cannot automatically be extrapolated to young children. Some investigations suggest that BIS may be valid in children older than 2 yr of age.²⁻⁶ Only one study, as far as we know, evaluated prospectively the correlation of BIS with end-tidal sevoflurane concentration in children.⁶ Regarding the effect of age on BIS values, there have been reports comparing the BIS between infants and children⁴⁻⁶ or between children and adults³ but there have been no reports comparing the BIS of young children and older children.

In this prospective randomized study we wanted to know if BIS values correlate with end-tidal concentration of sevoflurane (ETsevo), which is considered to reflect the anaesthetic depth. Additionally, the effect of age, in the range of 6 months to 12 yr, on BIS values was evaluated.

Methods

Institutional Review Board approval and informed consent from parents were obtained. Eighty-one, ASA I or II patients, aged 6 months to 12 yr, who were undergoing elective urology surgery lasting for more than 2 h (hypospadias repair, ureteroneocystostomy, orchiopexy, nephrectomy, etc.) were enrolled in the study. The patients who had a history of sleep apnoea, developmental delay, psychological disorder, or any neurological disorder were excluded.

Patients were not pre-medicated. Anaesthesia was induced with i.v. thiopental 5 mg kg⁻¹ and rocuronium 0.6 mg kg⁻¹ and the trachea was intubated. Anaesthesia was maintained with sevoflurane and nitrous oxide 60%
in oxygen. The monitoring consisted of ECG, NIBP, pulse oximetry, temperature, capnography, and end-tidal sevoflurane concentration. Neither opioids nor analgesics were used during induction or maintenance of anaesthesia. Lungs were mechanically ventilated and the ventilation was titrated to achieve an end-tidal carbon dioxide concentration between 4.0 and 4.6 kPa. After induction of anaesthesia, a paediatric BIS sensor (Aspect Medical System, Newton, MA, USA) was applied on the patient’s forehead; this was connected to an A-2000 BIS monitor (version XP: Aspect Medical System, Newton, MA, USA). Electrode impedances were found to be less than 2 kW before data acquisition started. The smoothing window was set at 15 s and the update rate at 2 s.

The patients were allocated into three age groups: 6 months to 2 yr, 3–7 yr, and 8–12 yr. At least 30 min after skin incision, sevoflurane was titrated to generate an end-tidal concentration (ETsevo) of 2.0, 3.0, and 4.0% in a stepwise increase or decrease pattern by computer generated random allocation in each age group. We avoided data collection when intense surgical stimulation was suspected. At least 15 min of equilibration time was allowed after each ETsevo (±0.1%) was reached and BIS values were recorded for another 15 min. The average of the consecutive 5 min average BIS values on BIS monitor was recorded as the BIS value at each ETsevo. All ETsevo were measured through a SOLAR® 8000 M monitor (General Electric Co., Wisconsin, USA) using a SAM®-Smart Anaesthesia Multi-gas Module (General Electric Co., Wisconsin, USA) to within an accuracy of 0.1%. The mean values of systolic arterial pressure (SAP), mean arterial pressure (MAP), and heart rate (HR) during steady-state ETsevo were also recorded. If necessary, some analgesics were used only after the completion of the study procedures.

**Statistical analysis**

A priori power analysis indicated that a total of 18 patients per group would be sufficient to detect a change in BIS of 10 with a power greater than 90% at the level of significance of <0.05. The Kolmogorov–Smirnov (K–S) test indicated that each variable followed a normal distribution. Therefore, parametric methods were used for all statistical analysis. Haemodynamic variables and differences in BIS level at each ETsevo within each group as well as among the three age groups were evaluated by two-way repeated measures ANOVA. Bonferroni correction was applied to the post hoc analysis. Non-linear regression analysis was used to examine the relationship between age and BIS in each steady-state ETsevo. All P-values are two-sided and are considered significant if P<0.05.

**Results**

Patients’ characteristics and surgical procedures are listed in Table 1.

**BIS and sevoflurane in children**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics. IQR, interquartile range</th>
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<tr>
<td><strong>Age</strong></td>
<td><strong>≥6 months</strong></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>28</td>
</tr>
<tr>
<td>Median age (IQR) (yr)</td>
<td>1.3 (0.89–1.7)</td>
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</table>

**Table 2 | Haemodynamic variables. Values are mean (SD). ETsevo, steady-state end-tidal concentration of sevoflurane. *P<0.05 vs values at ETsevo 2.0%** |
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<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Age groups</strong></td>
<td><strong>ETsevo 2.0%</strong></td>
<td><strong>ETsevo 3.0%</strong></td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>6 months to 2 yr</td>
<td>98.4 (16.7)</td>
<td>109.7 (19.5)</td>
</tr>
<tr>
<td></td>
<td>3–7 yr</td>
<td>105.0 (11.3)</td>
<td>107.6 (10.2)</td>
</tr>
<tr>
<td></td>
<td>8–12 yr</td>
<td>108.4 (13.5)</td>
<td>115.8 (15.8)</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>6 months to 2 yr</td>
<td>87.4 (8.3)</td>
<td>85.4 (10.2)</td>
</tr>
<tr>
<td></td>
<td>3–7 yr</td>
<td>99.0 (11.5)</td>
<td>94.6 (13.3)</td>
</tr>
<tr>
<td></td>
<td>8–12 yr</td>
<td>110.8 (13.1)</td>
<td>110.4 (14.5)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>6 months to 2 yr</td>
<td>64.4 (13.7)</td>
<td>57.0 (13.9)</td>
</tr>
<tr>
<td></td>
<td>3–7 yr</td>
<td>66.9 (11.1)</td>
<td>69.0 (13.8)</td>
</tr>
<tr>
<td></td>
<td>8–12 yr</td>
<td>84.8 (13.3)</td>
<td>82.0 (17.1)</td>
</tr>
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</table>

BIS decreased significantly when ETsevo changed from 2.0 to 3.0% but increased significantly when ETsevo changed from 3.0 to 4.0% in all age groups (Fig. 1); 57 of 81 of patients showed paradoxical increase in BIS values (>10%) as the ETsevo increased from 3.0 to 4.0%.

The non-linear regression analysis showed a significant correlation between BIS and age at each ETsevo. The younger patients showed the higher BIS values. Equations in all ETsevo are shown in Figure 2.

SAP and MAP did not change significantly as sevoflurane changed up to 4.0%. HR significantly increased at ETsevo 4.0% compared with HR at ETsevo 2.0% in all age groups (Table 2).

**Discussion**

One of the main findings of this study was that the BIS increased paradoxically as ETsevo increased from 3.0 to 4.0% and another is that the age itself can affect the BIS value in children aged 6 months to 12 yr.

There are some reports suggesting that the relationship between the MAC of sevoflurane and age in children differs from that of other inhalation agents. They insisted that the MAC of sevoflurane does not increase steadily as age decreases but it consists of only two values in children: 2.5% in infants aged 6 months to children aged 12 yr and 3.3% in neonates and infants of less than 6 months of age.78
This is the reason why we chose the age range of 6 months to 12 yr in this study. We assumed that the same concentration of sevoflurane would reflect the same MAC at all age groups. The 2.0–4.0% ET_{sevo} used in this study corresponds to 0.8–1.6 MAC of sevoflurane. Considering the effect of nitrous oxide on MAC of sevoflurane, this concentration with nitrous oxide 60% may approximate 1.1–2.2 MAC.

**Fig 1** BIS at three end-tidal sevoflurane concentrations in each age group. (A) 6 months to 2 yr; (B) 3–7 yr; (C) 8–12 yr. BIS decreased significantly as ET_{sevo} changed from 2.0 to 3.0% and increased significantly as ET_{sevo} changed from 3.0 to 4.0% in all three age groups (P<0.05).

**Fig 2** Non-linear regression analysis curves between BIS and age at each end-tidal sevoflurane concentration. (A) ET_{sevo} 2.0%: BIS=41.6+24.2×e^{-0.02×month}; R^2=0.313, P<0.001. (B) ET_{sevo} 3.0%: BIS=26.9+23.6×e^{-0.02×month}, R^2=0.518, P<0.001. (C) ET_{sevo} 4.0%: BIS=41.6+24.2×e^{-0.02×month}, R^2=0.313, P<0.001.
There has been only one study, as far as we know, about the correlation of BIS with ET$_{sevo}$ concentration in children. Denman and colleagues$^6$ demonstrated in 22 infants and children that the BIS decreased monotonically as the concentration of sevoflurane increased up to 4.0%. This result is somewhat different from ours. Our results showed a decrease in BIS only when the ET$_{sevo}$ changed from 2.0 to 3.0%, while the BIS increased when ET$_{sevo}$ changed from 3.0 to 4.0%. We do not know exactly what made this difference but hysteresis can be one of the explanations.$^{11,12}$ Previous workers used only downward sevoflurane concentration from 4.0% but we used both upward and downward sevoflurane concentration. Katoh and colleagues$^{13}$ studied the correlation of ET$_{sevo}$ and BIS in 69 adult patients. They showed that BIS decreased almost linearly with ET$_{sevo}$ increasing from 0.2 to 1.4% but sevoflurane concentrations greater than 1.4% up to 2.4% produced a limited further reduction of the BIS. There has been a report about paradoxical increases in the BIS with increasing isoflurane concentration.$^{14}$ In that study, there were significant increases in BIS in 40% of patients and unchanged BIS in 33% of patients during surgery when the end-tidal isoflurane concentration was increased from 0.8 to 1.6%. The authors proposed the possibility of paradoxical increase in BIS related to continuous pre-burst EEG patterns consisting of high-frequency activity. In our study, we cannot provide the reason why BIS paradoxically increased at high end-tidal sevoflurane concentration but the fact is that the BIS increased in 71.6% of patients when ET$_{sevo}$ changed from 3.0 to 4.0%. More importantly, in six patients (four in 6 months to 2 yr, two in 3–7 yr), the BIS value at ET$_{sevo}$ of 4.0% was over 60, which value can be falsely interpreted as light anaesthesia, without showing any other sign of light anaesthesia.

The pitfall of this study is that the surgical stimulations were not controlled. We did not use any other method for control of pain. Indeed, there have been reports showing that the surgical stimulations can alter the BIS values.$^{15-17}$ However, we started to record BIS values at least more than 30 min after the skin incision during the period of main procedure and also tried to avoid the data collection during the suspicious period of painful stimulations. The ET$_{sevo}$ of 3.0 and 4.0% with nitrous oxide 60% were sufficient to provide adequate depth of anaesthesia and there were no clinical signs of light anaesthesia. The arterial pressure decreased while BIS increased to ET$_{sevo}$ of 4.0%, but this increase in arterial pressure was not statistically significant. The HR increased (a small change of ∼11% when comparing HR at ET$_{sevo}$ 4.0% with that at ET$_{sevo}$ 2.0%) and this was regarded as the effect of sevoflurane itself rather than the sign of light anaesthesia.$^{18,19}$

Many studies have shown the usefulness of BIS in monitoring depth of anaesthesia but data have been limited and conflicting regarding the use of BIS in infants. Denman and colleagues$^6$ have shown that BIS values in awake and anaesthetized children and infants were comparable with the values in adults. However, Davidson and colleagues$^4$ found a wider range of BIS values and no ET$_{sevo}$ to BIS correlation in infants compared with children. Bannister and colleagues$^5$ found that the anaesthetic use was not reduced with the use of BIS. Although our results showed the similar pattern of BIS change in infants and children when the ET$_{sevo}$ changed from 2.0 to 4.0%, further evaluation would be necessary to determine the usefulness of BIS in infants or children under 2 yr.

The importance of age on the BIS values in paediatric patients has not been well documented. Some studies showed the validity of BIS in children older than 2 yr$^2$–$^6$ but no study showed the effect of age on BIS values in children, although it has been documented in adult patients.$^{20}$ It was concluded that increasing age reduced sevoflurane requirements to suppress responses to verbal command but did not change BIS.$^{20}$ In our study, however, the assumption was that the MAC is the same over the studied range of age and under that assumption, there was a strong correlation between BIS value and age. BIS value showed wide variation in the same ET$_{sevo}$ concentration in these paediatric patients and tended to be lower in older children.

In conclusion, we found that the value of BIS decreased when ET$_{sevo}$ changed from 2.0 to 3.0% but increased paradoxically when ET$_{sevo}$ changed from 3.0 to 4.0% in infants and children aged 6 months to 12 yr; in the same ET$_{sevo}$, BIS values showed a wide variation in the same ET$_{sevo}$ concentration in these paediatric patients and tended to be lower in older children.

Acknowledgement
The equipment used to collect the bispectral index data was on loan from Aspect Medical System, Newton, MA, USA (imported by Hippo Medical Co., Seoul, Korea).

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