The correlation of bispectral index with endtidal sevoflurane concentration and haemodynamic parameters in preschoolers

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Summary

Background: Bispectral index (BIS) is a signal processing device that potentially is a pharmacodynamic measure of the effects of anaesthesia on the central nervous system.

Methods: In this prospective blinded study, we investigated the pharmacodynamic relationship between BIS, haemodynamic changes during anaesthesia and endtidal nonsteady state concentrations of sevoflurane in 30 children, mean age 3.3 ± 1.1 years, who were undergoing tonsillectomy and adenoidectomy. A standardized anaesthetic technique was used and included induction and maintenance with sevoflurane, nitrous oxide and oxygen. BIS, heart rate, mean arterial pressure (MAP) and endtidal sevoflurane (ET$_{sevo}$) concentrations were continuously recorded and specifically noted at the time of intubation, placement of Dingman gag, incision of adenoid, adenoid out, incision of tonsil, tonsil one out, tonsil two out, last agent off, first spontaneous movement, first eye opening and extubation. The anaesthetist was blinded to BIS throughout the procedure.

Results: Using a Spearman correlation analysis, there was significant negative correlation between BIS and ET$_{sevo}$ concentrations ($r = -0.888, P < 0.01$) and a pharmacodynamic relationship with EC$_{50}$ (ET$_{sevo}$ at which BIS = 50) of 1.48% (95% confidence interval 0.84–2.11). There was a weak negative correlation between sevoflurane and MAP ($r = -0.391, P < 0.01$) but no significant correlation between sevoflurane and heart rate.

Conclusions: In preschool children undergoing sevoflurane anaesthesia for tonsillectomy and adenoidectomy, endtidal sevoflurane concentrations are more closely correlated with BIS than with MAP or heart rate.

Keywords: sevoflurane, bispectral index, haemodynamics, preschoolers; adenotonsillectomy

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Introduction

Bispectral analysis (BIS) of the electroencephalogram (EEG) is a signal processing technique that potentially is a pharmacodynamic measure of the effects of anaesthesia on the central nervous system (CNS) (1). BIS has been empirically demonstrated to correlate with behavioural measures of sedation and light anaesthesia in adult clinical utility studies and has been recommended as a monitor of consciousness levels during anaesthesia (1–3).

The variables commonly used to assess anaesthetic adequacy only provide indirect measures of the depth of anaesthesia. Autonomic nervous system responses, movement to surgical stimuli and end-tidal anaesthetic concentrations are all used to assess the depth of anaesthesia in children. However, if neuromuscular blocking agents are used, patient movement can no longer be used as an indication of anaesthetic depth. Haemodynamic responses can vary greatly from patient to patient and have been shown to be unreliable as measures of anaesthetic depth in adults (4–6).

Preschoolers as a group are less able than adults to report a complication of anaesthesia such as recall. Although the effects of intraoperative recall on preschoolers are unknown, it is possible that an unpleasant anaesthetic experience secondary to inadequate anaesthetic depth may be manifested as postoperative negative behavioural changes. It is known that premedicated children, who are amnesic about dental procedures, tolerate further dental procedures better than children who have memory about the procedure (7). For this reason, the BIS monitor may prove to be a helpful tool in ensuring that very young children are unconscious during anaesthesia. The BIS algorithm is derived from adult EEG data and the initial clinical utility and validation studies were performed only in adults. In a paediatric validation study, we have previously demonstrated that the BIS algorithm can be used in children older than 12 months of age (8). The aim of this utility study was to prospectively characterize changes in BIS using a standardized general anaesthetic technique and surgical procedure (tonsillectomy and adenoidectomy) in preschoolers and to correlate these BIS numbers with nonsteady state endtidal sevoflurane concentrations and the concurrent haemodynamic parameters that are routinely used to monitor the depth of anaesthesia during this procedure.

Patients and methods

After institutional review board approval and parental informed consent was obtained, 30 ASA I and II patients, aged 12–72 months, who were undergoing elective tonsillectomy and adenoidectomy, were enrolled. Patients were excluded if they had significant sleep apnoea defined as having an abnormal sleep study or an anticipated postoperative Intensive Care Unit admission for observation. Also, patients with cardiac, respiratory, neurological, hepatic or renal dysfunction were excluded as determined by history and physical examination.

Anaesthesia was standardized for all patients. No sedative premedication was given and all patients were induced by mask inhalation of sevoflurane, 70% nitrous oxide and 30% oxygen. Endtidal sevoflurane, ECG, pulse oximetry, noninvasive blood pressure, capnography and temperature were monitored during the anaesthesia. After intravenous cannulation, morphine (0.1 mg·kg⁻¹), cisatracurium (0.1 mg·kg⁻¹) and ondansetron (0.05 mg·kg⁻¹) were administered. Following tracheal intubation, ventilation was controlled to maintain an endtidal CO₂ level of 4.5–5.2 kPa (35–40 mmHg). At the conclusion of surgery, the neuromuscular blockade was reversed with neostigmine (0.07 mg·kg⁻¹) and glycopyrrolate (0.01 mg·kg⁻¹) and the anaesthetic gases were discontinued. During surgery, the anaesthetist assessed the depth of anaesthesia according to the patient’s haemodynamic response to the surgical stimulus and adjusted the depth of anaesthesia by altering the inspired sevoflurane concentration. The anaesthetist was blinded to the BIS numbers throughout the procedure and an independent study nurse recorded the data.

A disposable adult BIS Sensor (Aspect Medical Systems, Newton, MA, USA) was applied to the forehead of each patient after induction of anaesthesia and connected to a BIS A-1050 monitor (Aspect Medical Systems). The skin was prepared to insure low impedance and a good quality signal. The smoothing window was set at 30 s and the update rate was 2 s; BIS version 3.3 was used to analyse the raw EEG data. The BIS number was continuously recorded along with concurrent heart rate.
rate, mean arterial blood pressure (MAP) and non-
steady state endtidal anaesthetic concentrations. The
time of specific events (milestones) was noted by the
study nurse, specifically including time of intub-
ation, placement of the Dingman gag, incision of the
adenoids, tonsillar incision, tonsil one out, tonsil two
out, Dingman gag removed, neuromuscular block-
ade reversal, sevoflurane off, nitrous oxide off, patient
spontaneously moves, patient opens eyes, first
purposeful movement, tracheal extubation, move to postanaesthesia care unit (PACU) and discharge readiness. There were no BIS data recorded prior to the time of induction of anaesthesia, at the time of transfer to the PACU or at the time when the patients were assessed as ready for PACU discharge.

**Statistical analysis**

A correlation analysis between BIS and changes in
endtidal sevoflurane concentration, endtidal nitrous
oxide concentration, heart rate and MAP over time
was conducted using data from all perioperative
milestones except for induction, since the BIS Sensor
was placed after loss of consciousness. The Spear-
man rank correlation was used due to the nonlinear
nature of the BIS scale. This analysis was also
performed between the BIS value at the time that
the sevoflurane was discontinued and the timing of
emergence and discharge milestones.

Because of the multiple time points, four time
particular milestones representing induction, mainte-
nance and emergence from anaesthesia (intubation,
adenoid incision, tonsillar incision and first
purposeful movement) were chosen to evaluate
changes in BIS, endtidal sevoflurane, heart rate and
MAP at specific events. ANOVA with Bonferroni’s
correction was used after the Kolmogorov-Smirnov
Test had been performed to verify that the data were
normally distributed. \( P < 0.05 \) was considered statistically significant.

To determine a pharmacodynamic relationship
between BIS and endtidal sevoflurane concentration,
a calculation of the \( EC_{50} \), the endtidal sevoflurane
concentration at which BIS = 50, was constructed
using the equation of the inhibitory sigmoid \( E_{\max} \)
model:

\[
E = E_0 - \left[ E_{\max} C/\left(EC_{50}^c + C^c\right) \right]
\]

where \( C \) is the endtidal agent concentration, \( E \) is the
effect (BIS), \( EC_{50} \) is the agent concentration at a half-
maximal effect (BIS = 50) and \( \gamma \) is a shape para-
meter. \( E_{\max} \) is a scaling parameter that provides the
proper full-scale range (i.e. 0–100). Both \( E_0 \) and \( E_{\max} \)
were constrained to 100. The shape parameter \( \gamma \) was
set to 1. The data in this study are nonsteady state;
unwittingly misleading BIS results may be obtained when the
sevoflurane concentration changes rapidly. For this
reason, all data points between the time the sevo-
flurane was turned off and 5 min after the last
inhalational agent was turned off were excluded.
The resulting \( EC_{50} \) is expressed as a concentration
with a 95% confidence interval (CI).

**Results**

All enrolled patients (12 females and 18 males)
completed the study. All data collected from the
patients are presented; however, not all milestones
could be positively confirmed for every patient. The
patients’ age range was 1–6 years (mean 3.3 ±
1.1 years) and mean weight was 17.3 ± 3.4 kg.

BIS number, endtidal sevoflurane concentration,
mean arterial blood pressure and heart rate recorded at each milestone are shown in Table 1. Using
ANOVA for the four specified time points, we found
that there was a significant increase in BIS at the
time of first purposeful movement compared with
intubation and during maintenance of anaesthesia
\( (P < 0.05) \). MAP was also significantly higher at this
time \( (P < 0.05) \) but not heart rate. Both MAP and
heart rate increased significantly at the time of
tonsillar incision \( (P < 0.05) \), but without a signifi-
cant change in BIS or endtidal sevoflurane concen-
tration.

BIS and the endtidal sevoflurane concentrations
relative to intraoperative milestones, along with the
number of patients achieving each milestone, are
shown in Figures 1 and 2. There was a strong
negative Spearman rank correlation between BIS
values and sevoflurane concentrations \( (r = -0.888,
P < 0.001) \) at the milestone time points. The correla-
tion of BIS with \( N_2O \) in our study, although
statistically significant, was very weak \( (r = -0.437,
P < 0.001) \). There were weaker negative, although
significant correlations between BIS and MAP
\( (r = -0.320, P < 0.01) \) and between sevoflurane and
MAP \( (r = -0.391, P < 0.01) \). There was no significant
correlation between heart rate and sevoflurane concentration or between heart rate and BIS number. The BIS recorded at the time when the last anaesthetic agent was turned off positively correlated with the following recovery times: time to first response (r = 0.408, P = 0.039), time to open eyes (r = 0.552, P = 0.041) and time to extubation (r = 0.492, P = 0.012). An E_{max} pharmacodynamic model of BIS and endtidal sevoflurane concentration is shown in Figure 3. The model has an r^2 of 0.851 and an EC_{50} of 1.48% (95% CI 0.84–2.11).

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**Discussion**

In this study of preschoolers undergoing an identical surgical procedure and anaesthetic technique, we...
were able to demonstrate a significant correlation between a decrease in nonsteady state endtidal sevoflurane concentrations and an increase in BIS. A pharmacodynamic relationship was also determined with an EC$_{50}$ corresponding with a 1.48% endtidal sevoflurane concentration. We also found a significant positive correlation between BIS at the time of the last anaesthetic agent being turned off and recovery profile measures (i.e. time to first response, time to open eyes and time to extubation). In contrast, when comparing haemodynamic responses, there was only a weak correlation between endtidal sevoflurane concentrations and MAP and none between sevoflurane concentrations and heart rate.

We chose to study children undergoing tonsillec-
tomy and adenoidectomy based on our clinical experience that, while undergoing this type of surgery, children often experience haemodynamic changes (e.g. hypertension and tachycardia) during surgical stimulation, which can indicate an inadequate anaesthetic depth. However, haemodynamic signs in adults do not necessarily correspond to a specific consciousness level and haemodynamic responses to noxious stimuli are mediated at a subcortical level, and thus may be unrelated to the state of consciousness of an individual patient (3,4,9). Our data suggest that haemodynamic responses are an inexact indicator of consciousness levels in young children.

The correlation of BIS with N$_2$O in our study, although statistically significant, was very weak. Other studies in adults have demonstrated that BIS is not altered by the addition of N$_2$O to general anaesthesia (9,10). In this study, N$_2$O was not titrated during the anaesthetic but was maintained at 70% and thus a dose–response study of N$_2$O on BIS cannot be performed. However, because N$_2$O has been shown to have minimal effect on reducing MAC in young children, it may not contribute significantly to a change in the BIS number (11). A criticism of this study could be the inclusion of N$_2$O in the anaesthesia, which thus prevented the titration of BIS with a single inhalational agent. However, the aim of our study was to evaluate the clinical utility of BIS using a standard paediatric anaesthetic rather than perform a validation of BIS with a single inhalational agent.

The BIS algorithm was developed using several descriptors of the processed adult EEG that correlated with functional CNS suppression (level of consciousness) (1). These quantitative EEG parameters were chosen by multiple regression analysis of the raw EEG with empirical observation of adults undergoing sedation and anaesthesia (1). Each of the component EEG descriptors is related to a specific range of anaesthetic effect. The BIS algorithm accounts for the nonlinear nature of the EEG activity by allowing different parameters to determine the BIS number as the EEG changes its character with increasing anaesthetic depth. The BIS scale is nonlinear because the proportionate change observed in BIS for a change in hypnotic state is not constant across the entire BIS range, with BIS demonstrating a more gradual change at the extremes of the scale. Although the algorithm was developed using EEG data from adult subjects, BIS may be a reliable measure of the level of consciousness in children (8,10,11). For ethical reasons, it is more difficult to evaluate BIS in children than in adults. Pharmacodynamic measures of anaesthetic effect, such as movement on incision or memory and recall during sedation and anaesthesia, have been evaluated and correlated with BIS in adult volunteers but have not been evaluated in children (2,3,12). However, BIS values at emergence and at onset of loss of consciousness during paediatric anaesthesia have been studied (13,14). In addition to determining that haemodynamic values are not closely related to either endtidal sevoflurane concentrations or BIS, the results from our study, involving a controlled
anaesthetic and patient population, support the findings of previous paediatric and adult studies (2,3,8,13,14). These findings suggest that BIS may be an effective and accurate monitor of consciousness levels in children.

In an uncontrolled study of 77 children, aged 1 month to 12 years, who were undergoing a variety of general anaesthetics and surgical procedures, Denman et al. reported that BIS was a reliable measure of anaesthetic depth with no difference in BIS values found between children and adults during induction, maintenance and emergence (13). In our controlled study, the mean BIS number at milestone ‘first purposeful movement’ was 88 ± 11, which is similar to the mean BIS number reported by Denman et al. at emergence of anaesthesia (83.5 ± 11.6). Furthermore, using the $E_{\text{max}}$ model for pharmacodynamic effect, we calculated an EC$_{50}$ for BIS of 1.48% (95% CI 0.84–2.11) sevoflurane which is consistent with the EC$_{50}$ for BIS of 1.25% (95% CI 1.12–1.37) sevoflurane for children aged between 2 and 12-years old and 1.55% (95% CI 1.40–1.70) sevoflurane for infants (less than 2 years old), derived by Denman et al. (13).

The mean BIS number that we found at first purposeful movement is also consistent with the BIS results reported by Degoute et al. They examined BIS and the hypnotic component of anaesthesia induced by sevoflurane in 27 children and 27 adults who were undergoing tympanoplasty surgery (14). They reported a mean BIS number of 86.7 in children (mean age 8.6 years) for recovery of consciousness after verbal stimulus and they noted no difference between BIS values at time of loss of consciousness and emergence between children and adults (14).

In a utility study, Bannister et al. demonstrated that in patients aged 3–18 years who were undergoing tonsillectomy and/or adenoidectomy, BIS directed anaesthesia resulted in lower endtidal sevoflurane concentrations compared with those patients who did not have a BIS directed general anaesthetic (15). They also demonstrated a 25–40% decrease in measured recovery times. Of note, in children aged between 6 months and 3 years who were undergoing inguinal hernia repairs, they did not find any difference between the BIS directed general anaesthetics compared with standard anaesthetics with respect to anaesthetic use or recovery measures (15).

In a study designed to examine the validity of BIS in paediatric patients during circumcision surgery, Davidson et al. evaluated BIS and consciousness level during emergence from general anaesthesia (8). They reported a mean BIS of 73.5 ± 7 in children aged 1–14 years prior to arousal from a controlled verbal stimulus and a BIS of 83.1 ± 12 after arousal. Similar responses were noted in infants aged less than 12 months, although the BIS at arousal was found to be higher in children. In their study, the BIS was recorded up to 30 s prior to purposeful movement and the patients received no narcotics during their anaesthesia.

The effects of narcotics on BIS have not been studied in children but adult studies have shown that the adjunctive use of opioid analgesics can affect the use of BIS as a predictor of patient movement during surgery (3,16). When alfentanil was added to propofol sedation in adult volunteers, no effect on the steady state level of BIS was detected, but the change in BIS observed in response to a painful stimulus was attenuated (17). The BIS at arousal in children, whether or not they received adjunctive narcotics, was found to be similar to the BIS values at arousal for adults (2,13,14). This suggests that BIS in children measures the child’s hypnotic state regardless of whether he or she has received opioids as part of the anaesthetic. It is very possible that the morphine given prior to intubation attenuated the change in BIS that may occur during the painful stimuli while undergoing routine tonsillectomy and adenoidectomy.

We did not attempt to achieve a steady state endtidal sevoflurane concentration for BIS measurement at each milestone. This would have been difficult to accomplish during routine tonsillar and adenoid surgery without causing unnecessary delays. However, consistent with our study, Davidson et al. demonstrated a significant increase in BIS with decreasing endtidal sevoflurane concentration in children, but they were unable to demonstrate a similar relationship in infants (8).

The results reported from these previous paediatric studies of BIS, along with the findings of our study, support the utility of using BIS in children aged more than 1 year to titrate endtidal sevoflurane concentration and level of consciousness during anaesthesia. Further, our study demonstrates that haemodynamic responses do not closely correspond
with BIS and endtidal sevoflurane concentrations. However, further work is necessary before this form of monitoring can be recommended as an indicator of consciousness level across a range of anaesthetic techniques.

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References


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