Obstetrical and Pediatric Anesthesia

The bispectral index does not correlate with clinical signs of inhalational anesthesia during sevoflurane induction and arousal in children

[L'index bispectral ne correspond pas aux signes cliniques de l'anesthésie par inhalation pendant l'induction au sévoflurane et le réveil chez les enfants]

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Purpose: Validation of the bispectral index (BIS) in children requires correlating BIS with several levels of sedation, hypnosis and anesthesia. Our purpose was to compare BIS values with objective assessments of the level of hypnosis in children. We postulated that BIS predicted the level of anesthesia during induction and emergence in children.

Methods: In a prospective observational study, we evaluated the BIS monitor in 87 children (ages: 0.3 to 14 yr) ASA physical status I–II undergoing general surgery under sevoflurane and nitrous oxide. Clinical signs of inhalational anesthesia (CSA), the motor response to surgical incision and signs of arousal were used as indicators of the depth of anesthesia. CSA and BIS measurements were paired every minute during induction and emergence until arousal.

Results: CSA scores decreased during induction and increased during emergence ($P < 0.001$) and correlated with changes in sevoflurane concentrations ($r = -0.46$; $P < 0.001$). BIS was associated with changes in CSA scores during induction ($r = 0.49$; $P < 0.01$) and emergence ($r = 0.62$; $P < 0.01$), but the ranges of individual BIS values overlapped several levels of hypnosis. A BIS value greater than 50 had a positive predictive value of 25% for distinguishing between responders and non-responders to surgical incision. A BIS score equal or greater than 72 had a predictive value of 63% for discriminating between pre-arousal and arousal.

Conclusions: BIS correlates with several levels of hypnosis during inhalational induction and emergence in children, but individual BIS values show large inter-individual variability. The BIS monitor identified the physiological changes associated with arousal and distinguished the effects of preoperative sedation during emergence. The use of movement as an endpoint of hypnosis during surgical stimulation does not correlate with BIS values in children. The large inter-individual variability of BIS at different levels of anesthetic depth may limit the applicability of BIS to pediatric anesthesia.

Objectif : *La validation de l'index bispectral (BIS) chez les enfants exige la corrélation entre le BIS et quelques niveaux de sédation, d'hypnose et d'anesthésie. Nous voulions comparer les valeurs de BIS avec des évaluations objectives du niveau d'hypnose chez les enfants. Nous avons supposé que le BIS permettait de prédire la profondeur de l'anesthésie pendant l'induction et le retour à la conscience chez les enfants.*

Méthode : *Au cours d'une étude prospective par observation, nous avons évalué le moniteur de BIS chez 87 enfants de 0,3 à 14 ans, d'état physique ASA I-II, devant subir une intervention chirurgicale générale sous sévoflurane et protoxyde d'azote. Les signes cliniques de l'anesthésie par inhalation (SCA), la réponse motrice à l'incision chirurgicale et les signes d'éveil ont été les indicateurs de la profondeur de l'anesthésie. Les mesures des SCA et du BIS ont été pairées à chaque minute pendant l'induction et le retour à la conscience jusqu'au réveil.*

Résultats : *Les scores des SCA ont diminué pendant l'induction et augmenté pendant le retour à la conscience ($P < 0,001$) et correspondaient aux changements de concentrations de sévoflurane ($r = -0,46$; $P < 0,001$). Le BIS a été associé aux changements de scores des SCA pendant l'induction ($r = 0,49$; $P < 0,01$) et le retour à la*

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conscience (r = 0,62 ; P < 0,01), mais l'étendue des valeurs individuelles de BIS recoupaient quelques niveaux d'hypnose. Une valeur de BIS plus grande que 50 présentait une valeur prédictive positive de 25 % pour la distinction entre les répondants ou non-répondants à l'incision chirurgicale. Un score de BIS égal à 72 ou plus élevé avait une valeur prédictive de 63 % pour la discrimination entre le préréveil et le réveil.

Conclusion : *Le BIS correspond à quelques niveaux d'hypnose pendant l'induction par inhalation et le retour à la conscience chez les enfants, mais les valeurs individuelles de BIS montrent une grande variabilité interindividuelle. Le moniteur de BIS a enregistré les changements physiologiques associés au réveil et a distingué les effets de la sédation préopératoire pendant le retour à la conscience. Le mouvement utilisé comme paramètre de l'hypnose pendant la stimulation chirurgicale ne correspond pas aux valeurs de BIS chez les enfants. La grande variabilité interindividuelle du BIS à différents niveaux de profondeur d'anesthésie peut limiter l'applicabilité du BIS en anesthésie pédiatrique.*

SEVERAL quantitative attributes of the electroencephalogram (EEG) have been used to describe changes in the depth of anesthesia.[1,2] The bispectral index (BIS®) integrates time and frequency-domain analyses with quantitative measures of the harmonic and phase relations of several EEG frequency components.[2] It has been considered a replacement of physiologic variables for monitoring the depth of anesthesia. BIS values were derived from prospectively collected EEG in adults.[2,3] Thus, BIS parameters may not apply to the assessment of children.[3] Although initial studies indicate that BIS values correlate with changes in sevoflurane concentration during pediatric anesthesia,[4–6] results are difficult to interpret because no clinical endpoints of sedation or hypnosis were assessed.

The clinical validation of the BIS monitor during anesthesia in children requires correlating the BIS values with several levels of sedation or hypnosis, but this correlation may be associated with some limitations particularly in young children and infants.[4,5] The behavioural response of young children to verbal commands is often not reliable. Also, infants are typically uncooperative.[5,6] The evaluation of objective clinical signs[7,8] that change uniformly during inhalational induction such as the breathing pattern, eye movements, diameter of pupils and their reactivity to light, may provide a more reliable and valid assessment of the transition from awake to sleep in children. In addition, in the absence of muscle relaxants, the movement response to a standard stimulus such as skin incision and the purposeful response or eye opening during arousal may represent another objective means for explaining the effects of anesthetics.[8–10] In this study, we used these clinical signs as indicators of the changes in the level of hypnosis during sevoflurane anesthesia. We postulated that the BIS predicts an increasing depth of inhalational anesthesia during induction, and anticipates the manifestations of arousal during recovery from inhalational anesthesia.

Material and methods

Population

After approval from our institutional Ethics Review Committee and with parental informed consent, children of ASA physical status I or II undergoing non-cardiac and non-neurological surgical procedures and requiring elective general anesthesia, were enrolled in this prospective, observational study. Patients were excluded if they had significant cardiovascular, respiratory or neurologic disease or if they were taking chronic medication (e.g., methylphenidate) potentially affecting the EEG.

Premedication, if necessary, was achieved by midazolam (0.5 $mg \cdot kg^{-1}$). All patients had inhalational induction and maintenance under sevoflurane and nitrous oxide in oxygen (50/50). There was no use of muscle relaxant. Anesthetic management was performed by one of the three anesthesiologists participating in the study, who were blinded to the BIS results and the clinical assessment.

Clinical assessment

After proper consensus among the participating investigators, a three point-score scale was developed based on previously described clinical signs of inhalational anesthesia (CSA).[7–10] These clinical signs were classified into four categories (Table A, available as Additional Material at www.cja-jca.org) as follows: I) breathing pattern, II) eye movements, III) size of pupils and IV) pupillary response to light. In this study, it was assumed that patients with a maximum CSA score of 12 were awake, while those with a minimum score of 4 would be deeply anesthetized. Prior to the beginning of the study, two independent observers (R.A.R., S.D.) assessed the reliability of the scale in a group of children using evaluations every minute during induction and emergence until the child's spontaneous arousal. Arousal was defined when any of the following events first occurred: 1) purposeful movement of limbs, 2) facial grimace, 3) crying or phonating, or 4) spontaneous eye opening. Prearousal was defined as the last measurement prior to any manifestation of arousal. The end-tidal concentrations of sevoflurane and nitrous oxide, electrocardio-

gram, pulse oximetry, non-invasive blood pressure, capnography and temperature were monitored at every minute during induction and emergence.

Electrophysiologic assessment

In a subsequent phase of the study, we evaluated the association between the BIS and depth of anesthesia as indicated by the CSA scale. With the child awake, a disposable BIS-Sensor electrode (Aspect Medical Systems, Newton, MA, USA) was placed on the left forehead at locations corresponding to Fpz and F_7 grounded to the zygomatic arch and the system connected to the BIS processor module (software version 1.03.11en; Space Labs Medical, Mississauga, ON, Canada). The smoothing window was set at 15 sec and the update rate at two seconds. The EEG signals were band-passed using filters between 0.25 Hz and 70 Hz. The impedance for each electrode was maintained below 5 KΩ. The average BIS value from the last two 15-sec periods at the end of every minute was included in the analysis. "BIS arousal" was defined as the average BIS value within the first minute after arousal. BIS with a quality index below 25% were rejected. Prior to induction, baseline values consisting of a two-minute EEG recording, blood pressure and heart rate were established. Subsequently, nitrous oxide in oxygen (50/50) was delivered through a pediatric mask and this was followed by stepwise increases of sevoflurane (e.g., 3%, 5%, 8%) at fixed time intervals (approximately 15–20 sec) until loss of consciousness was achieved. At this time, a laryngeal mask airway (LMA) was inserted. Both electrophysiologic and clinical measurements were paired every minute from the start of induction until five minutes post-induction. For each measurement, clinical assessment was performed first, and the BIS value documented immediately after. Additional measurements recorded before and after the incision evaluated the response to surgical stimulation. The clinical response to incision was assessed by whether there was a gross, purposeful muscular movement of the child's head or extremities, twisting or jerking associated with the time of surgical incision. Some patients were administered a caudal epidural analgesic before incision with bupivacaine 0.25% (0.75–1.0 $mL \cdot kg^{-1}$) containing epinephrine (5 $\mu g \cdot mL^{-1}$). During surgery, the BIS values were concealed to the attending anesthesiologist. After completion of surgery and including application of dressings, the inhalational agents were discontinued, followed immediately by LMA removal and fresh oxygen (6 $L \cdot min^{-1}$) was delivered to the patient through a facial mask. The BIS and clinical assessments were assessed every minute from surgical completion to spontaneous arousal.

Data and statistical analyses

Variables were mostly non-normally distributed and results are presented as the median and quartile values (25th, 75th quartile). Blood pressure and heart rates during induction are expressed in percentages relative to pre-induction measurements, while those during emergence are correlated to the discontinuation of anesthesia. The use of relative rather than absolute values facilitated patients acting as their own control and minimized differences in age-related normative values and blood pressure cuff size. The changes on the BIS, heart rates, blood pressures and sevoflurane concentrations at different depths of anesthesia as indicated by the CSA scale were assessed by non-parametric Friedman tests. Wilcoxon-sign rank tests evaluated the differences between two related samples (e.g., pre-arousal and arousal), and the Spearman rank correlation determined the degree of association between BIS and clinical or hemodynamic measurements. Between-group differences (e.g., with and without preoperative sedation) were assessed by Kruskal-Wallis tests. The sensitivity and positive predictive value of BIS was calculated to determine its ability to distinguish between arousal and pre-arousal and between responders and non-responders to surgical stimulation. A $P < 0.05$ was considered significant. Our sample size was calculated under the assumption that a minimum of 50 patients would provide a 90% power (alpha = 0.05) to conclude that at least 80% of our population could show BIS values below 50 if the CSA scale decreased from 12 to 4.

Results

Patient characteristics

Seventy-seven of the 87 patients originally enrolled in the study completed the protocol. Exclusions were related to failure of displaying BIS values ($n = 3$) and blood pressures ($n = 4$) or to the child's non-cooperative behaviour ($n = 3$). The scale reliability was evaluated in 18 pediatric patients (ages: 3 to 14 yr) who had no preoperative sedation. The association between the BIS and CSA scale was evaluated in 59 children (ages: 4 months to 14 yr) including 21 premedicated and 13 that received caudal analgesia. Four of the 59 children were less than two years of age (two premedicated and one with caudal). No adverse effects were associated with placement of the BIS electrodes. The time between discontinuation of anesthesia and arousal was five minutes.[3,7] Surgical procedures included umbilical ($n = 6$) or inguinal ($n = 60$) hernia repair, orchidopexy ($n = 4$), circumcision ($n = 11$), removal of dermoid cyst ($n = 2$) or foreign bodies ($n = 4$).

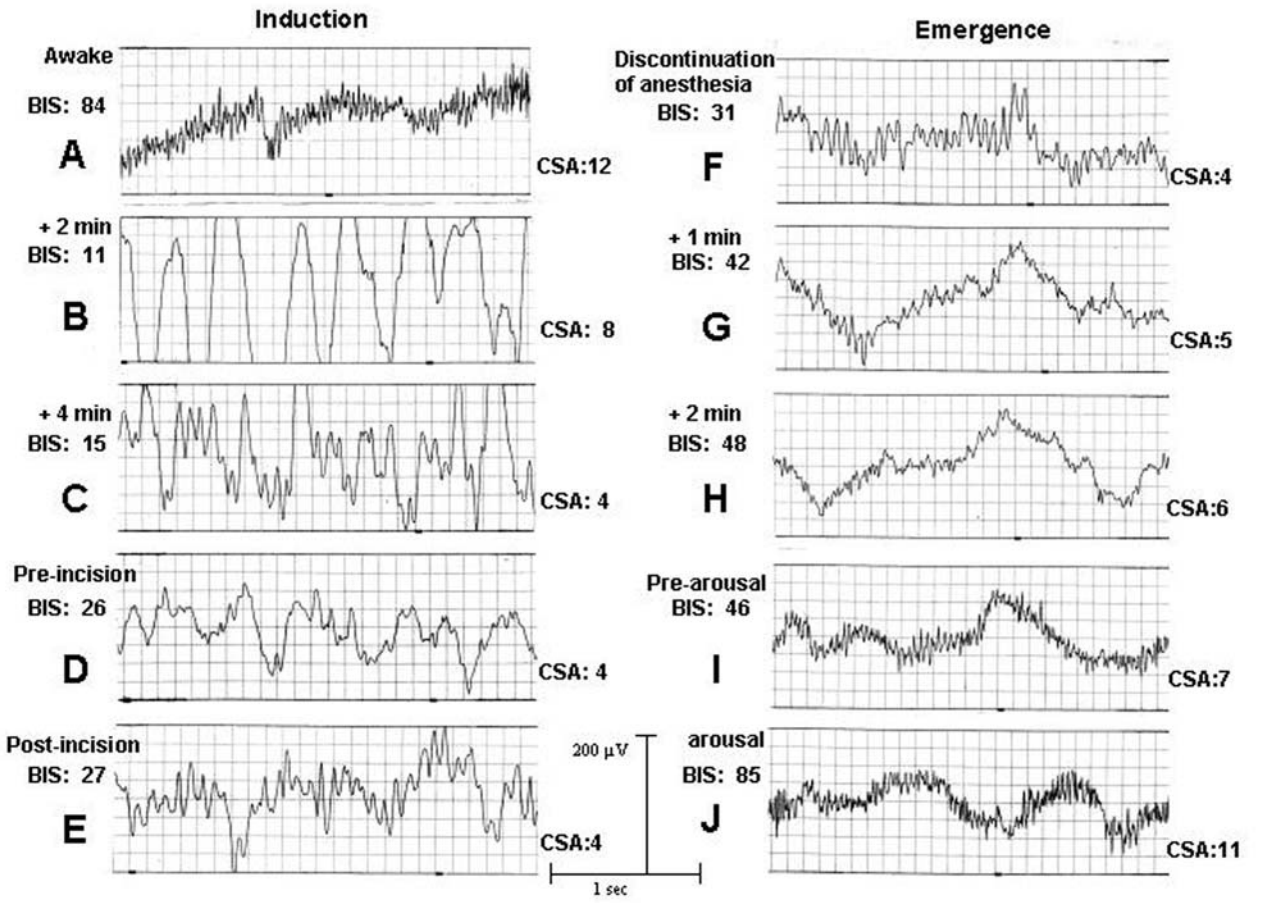

FIGURE 1 Left frontal electroencephalogram of a three-year-old child (premedicated) during inhalational induction (A-E) and emergence (F-J). The scores for the clinical signs of inhalational anesthesia (CSA) and the bispectral index (BIS) values corresponding to each trace are indicated.

Clinical assessment

CSA scores decreased ($P < 0.001$) during induction and increased ($P < 0.001$) during emergence. The changes in clinical signs correlated with the end-tidal concentrations of sevoflurane (r = -0.46; $P < 0.001$). The CSA scale showed an acceptable inter-observer correlation during induction (r = 0.83; $P < 0.001$) and recovery (r = 0.93; $P < 0.001$). From all categories, the breathing pattern showed the best inter-observer correlation during induction (r = 0.90; $P < 0.001$), followed by eyes position (r = 0.84; $P < 0.001$), size of pupils (r = 0.78; $P < 0.001$) and pupillary reactivity to light (r = 0.77; $P < 0.001$). In contrast, during emergence the inter-observer correlation was better than induction for all categories (r = 0.85, 0.88, 0.87, 0.89; $P < 0.001$). Figure A (available as Additional Material at www.cja-jca.org) shows the variability in clinical assessments between the two observers.

Electrophysiologic assessment

EEG FEATURES

In the majority of children, the EEG during induction and recovery showed changes similar to those illustrated in Figure 1. The EEG in an awake child (Figure 1, panel A) was characterized by a dominant fast frequency (> 13 Hz) and low-amplitude (< 50 µV) activity. Induction typically started with an increase in beta-range (> 13 Hz) activity and immediately changed to a slow EEG activity (< 8 Hz) with dominant large amplitude (> 400 µV) slow delta waves (< 2 Hz); (Figure 1, panel B). At deeper levels (Figure 1, panel C), the EEG gradually changed to a mixed spec-

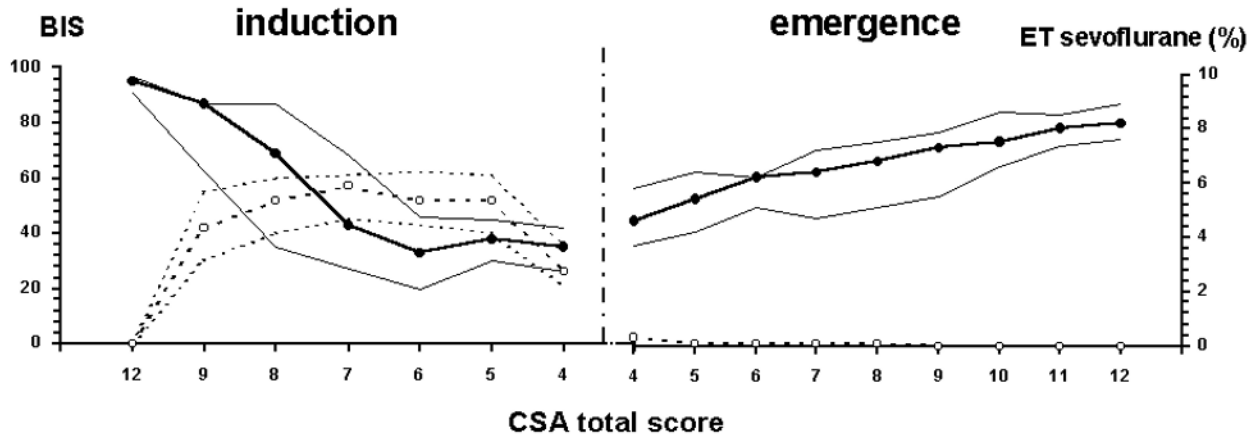

FIGURE 2 Changes in bispectral index (BIS; solid lines) and end-tidal (ET) sevoflurane concentration (dotted lines) during sevoflurane induction and emergence according to the clinical signs of inhalational anesthesia (CSA). Values represent the median (circles) and their 25th and 75th quartiles (lower and higher points) measured at every CSA score. In this study, it was assumed that patients with a maximum CSA score of 12 were awake, while those with a minimum score of 4 would be deeply anesthetized.

trum of medium frequency activity (6–10 Hz) with delta waves in the high-delta range (< 4 Hz). Typically, at CSA scores of 4, the EEG showed a steady-pattern of moderate amplitude (200–250 μV) rhythmic delta activity (< 4 Hz) intermixed with diffuse theta (< 8 Hz > 4 Hz) waves (Figure 1, panels D and E). Following discontinuation of anesthesia (Figure 1, panels G, H), the delta wave activity disappeared and the EEG spectrum shifted from slow (< 8 Hz) to fast frequency activity (> 13 Hz). Near-arousal (Figure 1, panel I), the EEG was characterized by a dominant fast activity with occasional bursts of diffuse theta (< 8 Hz > 4 Hz) waves. Finally, during arousal (Figure 1, panel J), fast activity (> 13 Hz) and frontalis muscle activity were the main components of the EEG activity. Seven children (aged: 2 to 9 yr) showed transient episodes of EEG burst suppression at rates that varied between 30% and 72%. Two patients (ages: 2 and 5 yr) had a discharge of multiple spikes during induction followed by a period of transient burst suppression with rhythmic polyspikes. No abnormal movements were seen and their recovery was similar to the rest of the group.

BIS and depth of anesthesia

INDUCTION AND SURGICAL STIMULATION

BIS correlated with the changes in clinical signs during induction ($r = 0.49$, $P < 0.01$). BIS decreased from median values of 95 (91, 97) to 33 (26, 42) between CSA scores of 12 and 4 (Table I; Figure 2). The BIS values obtained at CSA scores of 12, 8, 7, 5 and 4 were significantly different ($P < 0.05$). A CSA score of 4 was usually associated with lower BIS values, systolic blood pressures and heart rates compared with higher CSA scores. We observed that the range of BIS values overlapped between several levels of hypnosis (Table I) and that this resulted in a large inter-individual variability. For example, a BIS value of 77 that in one child corresponded to a CSA score of 6 was associated with a CSA score of 12 in another. This variability was more remarkable during the first two minutes of induction. The caudal block did not affect BIS [35 (22, 42) *vs* 41 (33, 53) $P > 0.05$] or clinical scoring (4 *vs* 4; $P > 0.05$). Skin incision [sevoflurane expired concentration: 2.2% (2.0, 2.9)] was related with noticeable movement in 9% of children. The BIS values in this percentage of patients were 42, 23, 34, 12, 63 and their respective CSA scores were 4, 4, 5, 6 and 5. No children with caudal anesthesia showed an incision-related motor response. All patients who did not respond to surgical stimulation had CSA scores of 4. After excluding patients who had additional caudal anesthesia, there was no difference in clinical assessment or BIS scores between responders and non-responders. In 94% of non-responders, BIS values were below 50 (range 10–49) prior to surgical stimulation. Based on these findings, a BIS value greater than 50 had 20% sensitivity and positive predictive value of 25% for differentiating between responders and non-responders to surgical stimulation.

Emergence and arousal

BIS was associated with changes in the depth of hypnosis during emergence (r = 0.62; $P < 0.01$). The BIS increased from 37 (32, 43) to 77 (65, 83); ($P < 0.001$) between discontinuation of anesthesia and arousal (Table II). In most children, a gradual and progressive increase in BIS values and CSA scores preceded arousal. BIS increased from pre-arousal [68 (57, 75); CSA: 7 (6, 9)] to arousal [77 (70, 85); CSA: 10 (8, 11); $P < 0.001$], but heart rates [-6% (-14%, +7%) *vs* 0% (-11%, +20%); $P > 0.05$] and systolic blood pressures [9% (0%, +14%) *vs* 12% (+2%, +17%); $P > 0.05$] remained unchanged. At arousal, 84% of children showed BIS values equal or greater than 61. These values corresponded to CSA scores equal or greater than 8. To differentiate between pre-arousal and arousal, a BIS value of 62 had 81% sensitivity and a positive predictive value of 53%. Increasing the BIS to a value of 72, slightly decreased the sensitivity (71%), but it increased the positive predictive value to 63%.

Premedication and age

Preoperatively sedated children [3 yr (2, 4)] were younger than non-sedated [7 yr (4, 9); $P = 0.001$]. Prior to induction, the BIS of sedated patients [95 (91, 97] were similar to those of non-sedated [96 (91, 97); $P = 0.61$], but the BIS values in sedated patients prior to arousal were significantly lower [61 (45, 75)] than non-sedated [71 (62, 77); $P = 0.02$]. These differences were non-significant at arousal [76 (56, 85) *vs* 79 (70, 85); $P = 0.44$]. The use of premedication in children did not show differences in the time to arousal compared with non-premedicated patients [5 min (4, 6) *vs* 5 min (4, 6)]. There was no association between age and BIS values during awake (r = -0.37; -0.01; $P > 0.09$), pre-arousal (r = 0.39; -0.13; $P > 0.08$) and arousal (r =-0.10; -0.06; $P > 0.50$) in premedicated and non-premedicated patients.

Discussion

We found that BIS values are associated with changes in the depth of hypnosis during sevoflurane induction in children as indicated by quantitative assessments of

TABLE I Induction. BIS and hemodynamic variables recorded at different levels of hypnosis (CSA scale)

CSA	*n*	*BIS*	*Systolic blood pressure (%)*	*Heart rate(%)*	*Sevoflurane(end-tidal %)*
12	59	95 (91,97) [77 to 98]*	0	0	0
9	3	87 (62,87)[62 to 87]	-10	-10	4.2 (3.0,6.0)
8	31	69 (35,87) [9 to 97]*	-2 (-13,+6)[-36 to +32)	-2 (-15,+10)[-27 to +55]	5.7 (4.0,6.0)[2.0 to 8.0]
7	57	43 (27,68)[7 to 98]	0 (-14,+11)[-50 to +73]	0 (-14,+11) [-35 to +90]*	5.3 (4.4, 6.0)[2.0 to 8.0]
6	49	33 (20,46)[7 to 98]	+2 (-15,+10)[-34 to +69]	-2 (-15,+10) [-35 to +87]*	5.2 (4.3, 6.1)[1.0 to 7.0]
5	53	38 (30,45) [8 to 63]*	+1 (-13,+14) [-34 to +69]*	+1 (-13,+14)[-40 to + 82]	5.2 (4.0, 6.1)[2.0-7.0]
4	123	35 (26,42)[8 to 68]	+13 (-20,-3)[-47 to +41]	-13 (-20,-3)[-35 to +99]	2.6 (2.1, 3.5)[1.0 to 7.0]

Values are median (25th quartile, 75th quartile); range [minimum, maximum value]; heart rate and systolic blood pressure are expressed in percentage of change relative to pre-induction values (CSA: 12); BIS = bispectral index, CSA = clinical signs of inhalation anesthesia; CSA scores of 11 and 10 are not included because no clinical assessment resulted in such scores during induction; *n* = number of clinical assessments for each individual CSA score; *Statistically significant at $P < 0.05$ compared to the subsequent level of hypnosis in the direction from CSA scores of 12 to 4.

TABLE II Emergence. BIS and hemodynamic variables recorded at different levels of hypnosis (CSA scale)

CSA	*n*	*BIS*	*Systolic blood pressure (%)*	*Heart rate(%)*
12	29	82 (76,89)[66 to 97]	+13 (+2,+24)[-26 to +43]	+13 (-13,+25)[-12 to +53]
11	20	80 (74,85)[50 to 98]	+13 (+2,+21)[-26 to +56]	+1 (-7,+26)[-22 to +51]
10	24	75 (66,86)[46 to 97]	+11 (+5,+21)[-9 to +69]	+8 (-11,+25)[-16 to +50]
9	20	73 (55,79)[37 to 89]	+8 (-1,+23%)[-34 to +34]	+17 (-4,+24)[-20 to +51]
8	37	68 (51,75)[42 to 98]	+5 (-1,+10)[-10 to +28]	-5 (-15,+2) [-23 to +35]*
7	35	64 (47,72)[39 to 90]	+2 (-6,+13)[-19 to +23]	-6 (-12, -1)[-30 to +26]
6	52	62 (51,59)[29 to 85]	+5 (-1,+12)[-19 to +23]	-4 (-9,+2)[-23 to +46]
5	70	54 (42,64) [21 to 74]*	+2 (-1,+10)[-9 to +31]	-5 (-9, 0)[-24 to +7]
4	107	46 (37,58) [23 to 86]*	0 (0,+6)[-37,+24]	0 (-4, 0) [-21 to +5]*

Values are median (25th quartile, 75th quartile); range [minimum, maximum value].

BIS = bispectral index; CSA = clinical signs of inhalational anesthesia; Heart rate and systolic blood pressure are expressed in percentage of change relative to the discontinuation of inhalational anesthesia; *n* = number of clinical assessments for each individual CSA score.
*Statistically significant at $P < 0.05$ compared to the subsequent level of hypnosis in the direction from CSA scores of 4 to 12.

the breathing pattern, eye position, size of pupils and the pupillary response to light. In addition, we observed that subjects' BIS values overlapped between several levels of anesthesia and consequently, this resulted in large inter-individual variability. Our findings are similar to previous investigations indicating that BIS values overlap between different levels of sedation in adults during regional anesthesia,[11] in patients of critical care units[12] and in volunteers during physiologic sleep.[13]

Several factors may be associated with the variability of BIS values in our study. Inhalational induction involved rapid changes of the inspired concentration of sevoflurane, which did not represent steady-state measurements. A previous study[4] indicated that minimum alveolar concentrations (MAC) of sevoflurane are higher in infants compared to children. We observed frontalis muscle activity particularly at initial stages of induction, which has been described to potentially corrupt the BIS calculations.[3] Some of our patients had periods of EEG burst suppression. A previous report[14] suggests that the BIS algorithm during those episodes is insufficient to calculate accurately the BIS values and paradoxical increases in BIS values may be expected as a result of increases in anesthetic concentrations. We suspect that the time for computation of BIS scores is critical during induction in children. BIS scores resulting from longer computational times may not accurately reflect the faster changes in anesthetic concentration or clinical signs. Although there was no effect of age on BIS values, it is known that the EEG in the pediatric population shows maturational changes with age and that the effects of sedation on the EEG are particularly more pronounced in younger children.[15] In addition, it is recognized that a smooth transition from awake to physiologic sleep may not occur in young children as compared with adults and this may result in a sudden drop into deep sleep with the consequent omission of transitional stages on the EEG.[15,16]

In our investigation, children who moved in response to surgical incision had pre-incision BIS values lower than 50 except for one (BIS: 63). It is expected that lower BIS values indicate a low probability of motor response during incision,[3,17] but our findings suggest that low BIS values in children do not guarantee the absence of a motor response during surgical stimulation. Katoh *et al.*[18] indicated that BIS was not a significant predictor of movement in response to skin incision under sevoflurane. It is assumed that the apparent failure of the BIS for predicting movement may be associated to differences in the anatomical sites responsible for the motor response (e.g., spine) as compared with the neural structures generating the EEG (e.g., cortex).[2,3]

There was a 9% incidence of movement in response to surgical stimulation. Although the rate appears to be high, we speculate that these findings may be related either to the non-caudal group not receiving supplemental analgesia or to the highly sensitive method of detection used in our study. The concomitant use of regional anesthesia in some of our patients introduced a confounding variable in the assessment of the motor response to surgical incision. None of our patients with caudal analgesia moved in response to skin incision. Moreover, no changes in BIS values were found between before and after the caudal administration. These results appear to be in agreement to those of Morley *et al.*[19] and Ibrahim *et al.*[11] who did not find any changes in the BIS values of adults following epidural anesthesia, but another study[20] found a decreased anesthetic requirement following epidural blockade suggesting a moderate but significant effect on inhalational anesthetic requirements.

Two of our patients without history of neurologic symptoms had a discharge of multiple spikes during induction. Previous reports[21–23] indicate that this phenomenon may occur in a small number of adult and pediatric patients under sevoflurane induction. Although the factors involved with these events are not clear, it has been reported that adult patients who had controlled hyperventilation or faster induction are more likely to show these alterations compared with those under normal ventilation or slower induction.[23]

In our study, BIS increased from the discontinuation of inhalational agents to arousal. This was the consequence of disappearance of the slow waves and increase in the high frequency activity of the EEG (30–40 Hz). Similarly, Degoute *et al.*[24] found an increase in BIS during recovery of sevoflurane anesthesia in children, but their BIS values during arousal were slightly higher than those found in our study. The discrepancy may be related to the use of different scales for assessing the level of hypnosis and to differences in anesthetic requirements associated with the type of surgeries included in their study.

Our study has limitations. We used adult BIS sensor electrodes because a pediatric version was not available. We found that these electrodes are not suitable for children. It is possible that this may have accounted for misplacement of the electrodes in some of our cases and failure to display BIS values. There was variability attributed to the use of premedication.[25] Our analysis stratified patients based on whether they received premedication, however, the effects of initial sedation in these patients cannot be distinguished from the sevoflurane effect. We did not evaluate BIS and CSA scores at steady-state anesthetic

concentrations. Thus, any attempt to correlate these two variables with MAC is inappropriate. In addition, our patients were not followed postoperatively and this precluded correlating intraoperative BIS values with postoperative recall.

Our study incorporated previously described clinical signs of inhalational anesthesia because changes in the level of consciousness associated with inhalational induction are faster[8–10] and these signs appear to be more consistent than the child's behavioural response. Our findings indicate that CSA scores had a fair correlation with end-tidal sevoflurane concentrations (r = 0.46). Although Cullen *et al.*[7] used these clinical signs for halogenated agents different from sevoflurane, clinical eye signs at induction are described as reliable indicators of the level of anesthesia under sevoflurane.[10] The latency between initial induction and changes in several eye signs appears to correlate with the different stages of sevoflurane induced sleep as determined by the EEG.[10] Moreover, the maximum level of EEG depression has been associated with reductions in pupil size or reactivity, and apnea.[26,27] Nevertheless, the applicability of our clinical assessment for agents different from sevoflurane will have to be determined.

In summary, BIS correlates with several levels of hypnosis during inhalational induction and emergence in children, but individual BIS values show large inter-individual variability. This variability may be influenced by several factors such as age, type of anesthesia, non-steady state anesthetic concentrations, preoperative sedation, time for computation of the BIS algorithm, frontalis muscle activity, degree of EEG burst suppression and clinical assessment. The BIS monitor identified the physiological changes associated with arousal and distinguished the effects of preoperative sedation during emergence. The use of movement as an endpoint of hypnosis during surgical stimulation does not correlate with BIS values in children. The large inter-individual variability of BIS at different levels of anesthetic depth may have implications for the applicability of BIS to pediatric anesthesia. Further studies correlating BIS and clinical endpoints of hypnosis are necessary prior to determine whether current BIS versions are applicable to pediatric anesthesia.

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