Validation of the Bispectral Index Monitor for Measuring the Depth of Sedation in Children

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The Bispectral Index (BIS) is an empirically calibrated number derived from adult electroencephalograph data that correlates with the depth of sedation in adults. We tested the hypothesis that the BIS score is a valid measure of the depth of pediatric sedation in a study designed to avoid limitations of a previously published report. BIS values from 96 healthy ASA physical status I–II children aged 1–12 yr undergoing sedation were continually recorded and electronically transferred to a computer. Two independent observers blinded as to BIS score evaluated sedation using the Observer's Assessment of Alertness/Sedation (OAA/S) and the University of Michigan Sedation Scale (UMSS) at 3–5 min intervals. There was a significant correlation between BIS and UMSS and between BIS and OAA/S by both the Spearman's rank correlation test and by prediction probability ($P < 0.001$). In children <6 yr, there was a significant correlation between BIS and the clinical sedation scores for subgroups undergoing invasive and noninvasive procedures ($P < 0.001$). There was also good agreement between the 2 independent observers who assessed clinical sedation scores (kappa = 0.51, $P < 0.001$). We conclude that the BIS monitor is a quantitative, nondisruptive and easy to use depth of sedation monitor in children.

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Both the American Society of Anesthesiologists and the American Academy of Pediatrics recommend systematic monitoring of the depth of sedation in children (1–3). However, validated tools for measuring sedation in children, such as the University of Michigan Sedation Scale (UMSS) (4) and the Observer's Assessment of Alertness/Sedation (OAA/S) scores (5,6), have limitations in clinical practice because of observer variance in the subjective assessments and the disruptive effect of stimuli that need to be given to assess the depth of sedation. The Bispectral index (BIS) monitor is an objective, quantitative method of assessing the level of sedation in adults, where the BIS value is a single dimensionless, empirically calibrated number ranging from 100 indicating an awake, alert status to 0 representing an isoelectric electroencephalographic (EEG) pattern (7–10). Studies of the use of BIS in anesthetized children suggest that there are age-related differences, indicating that BIS values based on adult EEG data may not directly apply to the pediatric population (11,12). An editorial has recommended that the validation of the BIS monitor in children of different age groups should be a priority before trials are performed to determine its clinical use in children (13). One study has attempted to validate the use of BIS for evaluating the depth of sedation in children (14). This validation study has been criticized for a study design that involved the use of only a single observer who was not blinded as to BIS values, the application of variable intensity stimuli to assess depth of sedation, and comparisons with BIS scores obtained after stimulation (15). We tested the hypothesis that the BIS is a valid objective measure of the level of sedation in children younger than 12 yr of age using a study design to avoid the limitations of the previous study (14).

Methods

Ninety-six healthy ASA physical status I–II children aged 1 to 12 yr were enrolled in this observational study after obtaining IRB approval, parental written informed consent, and age-appropriate assent from

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Table 1. Demographic Data

	1-6 yr noninvasive procedures (n = 30)	1-6 yr invasive procedures (n = 32)	6-12 yr invasive procedures (n = 34)
Age	2.1 ± 0.7	2.8 ± 1.6	9.1 ± 2.1
Gender			
Male	14	21	19
Female	16	11	15
Procedure			
Biopsy—renal, liver or skin	0	3	3
CT scan	18	0	0
Transthoracic echocardiography	5	0	0
EMG	0	2	1
GI endoscopy	0	19	21
Insertion PICC or other central lines	0	7	8
Joint injection	0	1	1
Radionuclide scan	4	0	0
Ultrasound scan	3	0	0
Sedative Drugs			
Chloral hydrate—oral	9	0	0
Meperidine + promethazine—intramuscular	0	3	1
Midazolam + fentanyl IV	3	21	24
Pentobarbital + midazolam + fentanyl—IV	18	8	9

Age is presented as mean ± SD. Other data are presented as the number of children in each group.
EMG = electromyography; GI = gastrointestinal; CT = computerized tomography; PICC = peripherally inserted central catheters.

the child. We excluded children with severe developmental delay, known neurological disorders such as hemiplegia, demyelinating disorders, airway abnormalities, marked skin sensitivity, and conditions where the placement of the sensor or process of assessment would interfere with the procedure (e.g., magnetic resonance imaging). We also excluded children receiving general anesthesia or ketamine and those with an endotracheal tube in place. Children underwent sedation administered by nonanesthesiologists for invasive and noninvasive diagnostic or therapeutic procedures in the gastrointestinal endoscopy suite, computerized tomography scanner, interventional radiology suite, or the minor procedure suite at a tertiary care children's hospital. Sedation medications varied among departments (Table 1) and were not controlled by the study protocol but were administered under the supervision of the attending physician who was not an investigator of the study, and the dose was titrated according to the individual patient's need.

An age and head size-appropriate disposable BIS sensor (standard pediatric or XP sensor, Aspect Medical Systems, Newton, MA) was placed on each child's forehead and connected to a BIS monitor (Model A2000, BIS algorithm revision 4.0) as directed by the manufacturer. The protocol required the sensor to be placed as early as possible, preferably before sedation; although some small patients would not cooperate for sensor placement before the administration of sedative drugs. In all cases the sensor was placed before the procedure began. The BIS monitor screen was covered during the procedure to ensure that all personnel involved in performing the diagnostic or therapeutic procedures, in administering sedation medications, and the two independent observers were blinded as to the BIS score. These two observers evaluated sedation using the OAA/S and the UMSS at 3–5 min intervals. The UMSS score is a 5-point observational scale for the depth of sedation: 0 = awake and alert, 1 = minimally sedated (tired/sleepy, appropriate response to verbal conversation and/or sound), 2 = moderately sedated (somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command), 3 = deeply sedated (deep sleep and arousable only with significant physical stimulation), 4 = unarousable (4). OAA/S scores were recorded at the same time epochs by the two observers using the original OAA/S scale (5), where smaller values indicate more intense sedation (in contrast to the UMSS score). Both UMSS and OAA/S have been widely used and validated for measuring the depth of sedation in children (4–6).

The two observers assessing sedation using UMSS and OAA/S scales did not communicate their assessment to those performing the procedure and administering sedative medications. Both observers separately noted the time, dose, and responses of the patients manually in their datasheets, and one observer also recorded the doses and times of administration of sedation medications, and patients' responses to stimulation in real time in the computer.

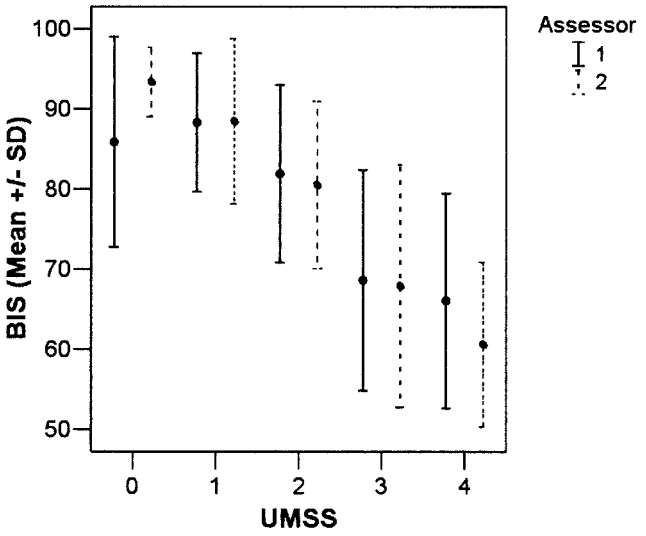

Figure 1. Inter-rater reliability of the University of Michigan Sedation Scale (UMSS) scores and correlation with the Bispectral index (BIS). There was a good inter-observer reliability (Kappa = 0.51, $P < 0.001$)

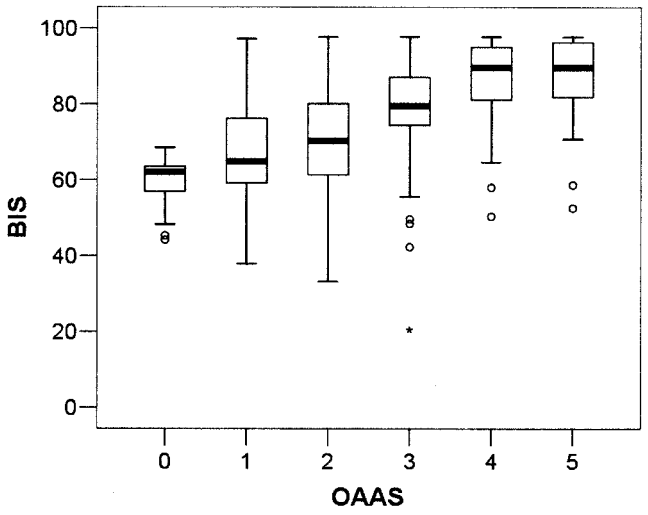

Figure 2. Correlation between Bispectral index (BIS) and Observer's Assessment of Alertness/Sedation (OAA/S) scores in all 96 patients ($r = 0.59$, $P < 0.001$).

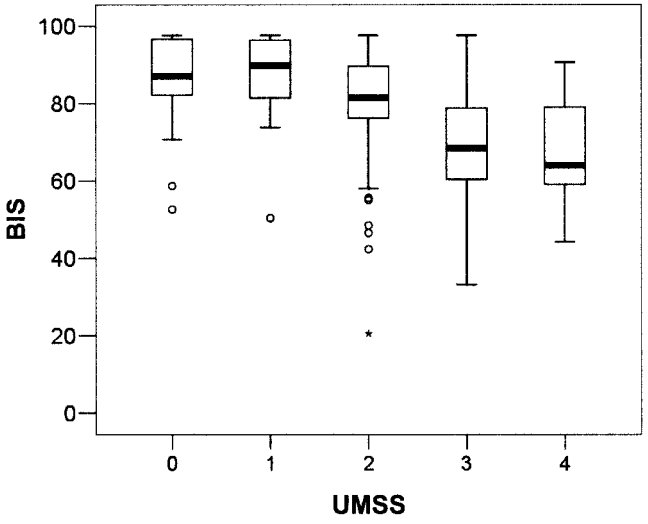

Figure 3. Correlation between Bispectral index (BIS) and the University of Michigan Sedation scale (UMSS) in all 96 patients ($r = 0.56$, $P < 0.001$).

Data from the BIS monitor, including BIS values, electromyographic (EMG) activity, EEG, and signal quality were continually recorded and electronically transferred to this computer. The average BIS scores over a 40-s time period just before the application of a standard-intensity stimulus (stroking the back of the patient) for depth of sedation evaluation were downloaded from the computer for statistical analysis. BIS values with poor signal quality and high EMG scores were rejected for the analysis.

Correlation between paired UMSS and BIS, and OAA/S and BIS scores were determined by applying the Spearman rank correlation test. In addition, the prediction probability was calculated as a measure of the association between the BIS values and the clinical sedation scores. Prediction probability values near 1 indicate very close relationships, scores near 0.5 suggest no relationship, and scores near 0 suggest a strong inverse relationship (16). BIS scores were divided into ranges of <50, 50–59, 60–69, 70–79, 80–89, and 90 or higher. The γ statistic was used for correlating the ranged BIS score with specific UMSS and OAA/S scores.

The kappa statistic was used to analyze the inter-rater reliability for UMSS and OAA/S scores. A multivariate analysis was performed with the BIS values as the dependent variable and age, gender, sedative drugs, and OAA/S and UMSS scores as the independent variables. $P < 0.05$ was considered to be statistically significant.

Results

Sixty-two of 96 children were <6 yr old, 30 underwent noninvasive and 32 invasive procedures. There were no significant differences in the demographic data including age, gender, and weight in these two groups. The other 34 children who were >6 yr age underwent invasive procedures with sedation. Patients received sedation with oral chloral hydrate, IM meperidine and promethazine, IV pentobarbital, fentanyl, midazolam or a combination of these sedatives (Table 1).

A total of 647 paired data points (clinical sedation scores and BIS values) were analyzed (Figs. 1–3). There was good agreement between the 2 independent observers who assessed clinical sedation scores (Fig. 1) (kappa = 0.51, $P < 0.001$, prediction probability was 0.849 for UMSS scores and 0.859 for OAA/S scores respectively, $P < 0.001$). There was a significant

Table 2. Bispectral Index

	UMSS scores					OAA/S scores					
BIS values	0	1	2	3	4	0	1	2	3	4	5
<50	0	0	4	34	3	3	12	22	4	0	0
50–<60	2	1	3	43	3	3	15	27	3	2	2
60–<70	0	0	10	101	6	7	31	65	12	2	0
70–<80	2	10	66	90	2	0	27	59	66	16	2
80–<90	7	26	70	45	3	0	9	43	46	42	11
90–100	8	37	50	20	1	0	1	15	31	57	12

The Bispectral Index (BIS) data are reported as the number of data points at each UMSS and OAA/S score. These correlations between BIS versus UMSS (gamma = 0.66, $P < 0.001$) and BIS versus OAAS (gamma = 0.61, $P < 0.001$) were statistically significant.
UMSS = University of Michigan Sedation Scale, OAA/S = Observer's Assessment of Alertness/Sedation.

correlation between BIS and OAA/S (Fig. 2) (Spearman's rank correlation $r = 0.59$, $P < 0.001$) (Fig. 2) and between BIS and UMSS ($r = 0.56$, $P < 0.001$) (Fig. 3). The prediction probability between BIS and UMSS was 0.285 and 0.287 for observers 1 and 2, respectively ($P < 0.001$), whereas the prediction probability between BIS and OAA/S scores was 0.723 and 0.722 for observer 1 and 2, respectively ($P < 0.001$). There were 351 BIS values obtained when both observers were in agreement for the UMSS and OAA/S scores. When the analysis was limited to these values, the prediction probability was 0.253 for the BIS and UMSS scores and 0.755 for the BIS and OAA/S scores. In contrast to the UMSS scale, low scores in the OAA/S indicate more intense sedation. The prediction probability for UMSS and OAA/S response was 0.072 for observer 1 and 0.086 for observer 2.

In children <6 yr, there was a significant correlation between the BIS values and the clinical sedation scores for subgroups who had invasive and noninvasive procedures ($r = 0.56$ for invasive and 0.37 for noninvasive procedures, $P < 0.001$ for both). As all children older than 6 yr underwent invasive procedures, a subgroup comparison was not possible for the older child. The BIS values were strong predictors of the OAA/S and UMSS scores and independent of age, gender, and sedative drug used. The correlations between the ranged BIS values with UMSS ($\gamma = 0.66$, $P < 0.001$), and with OAAS ($\gamma = 0.61$, $P < 0.001$) were statistically significant (Table 2).

Discussion

The results of this study demonstrate that the BIS may be a valid monitor of the depth of sedation in children undergoing invasive and noninvasive procedures. BIS scores correlated significantly with their paired UMSS and OAA/S scores. The BIS has several potential advantages over observational clinical sedation scoring systems: it is objective, quantitative, free from observer bias, easy to use, and does not require the use of stimuli that can result in patient responses that disrupt the procedure for which children are sedated. Our results are consistent with the findings of McDermott et al. (14) indicating inter-institutional reliability and potential universal application. The strength of our study compared with the previous validation study is that it is a blinded study, where two independent observers assessed sedation using two validated clinical sedation assessment scales, UMSS and OAA/S. In addition, we used direct real time electronic transmission of BIS data to avoid observer bias and excluded patients receiving ketamine, which results in sedation at high BIS values; thus we avoided a potentially confounding factor in the analysis. Another strength of our study is that we tested the validity of BIS in a wider spectrum of sedation in three clearly defined subgroups, from sedation for noninvasive to more invasive procedures, with about two thirds of children <6 years of age. The sedative drugs we used ranged from chloral hydrate for mild sedation to combinations of fentanyl, midazolam, and pentobarbital for deeper sedation. We also used prediction probability, a statistical technique that has been recommended as the appropriate measure for evaluating and comparing the performance of anesthetic depth indicators (16).

A major problem in the validation of the BIS monitor as an assessment of the depth of sedation is the absence of a "gold standard" for comparison. A number of clinical scoring systems have been used in adults and modified for use in children, but their validity has not been clearly established (17–19). In this study, we used the UMSS and OAA/S, as both scales had been successfully applied and validated for measuring the depth of sedation in children (4–6). However, these scales are subject to inter-observer variability, particularly in the middle portion of the scale (4). This may explain the wide scatter of BIS values at various sedation scores. When the analysis was limited to points where the 2 observers were in agreement about the clinical sedation score, there was a closer association between BIS values and the sedation scores, as demonstrated by the prediction probability.

These clinical scoring systems have a major disadvantage, as they require the additional application of verbal or noxious physical stimuli to assess the level of

sedation during the clinical procedure for which the sedation was administered. Clinicians are understandably reluctant to apply vigorous physical stimuli (to assess the level of sedation using clinical sedation scales) to children, especially those undergoing less than deep sedation for noninvasive procedures, such as transthoracic echocardiography and computerized tomographic scanning, as the accompanying patient response of undesirable movements, hemodynamics, and physiological changes could defeat the purpose of sedation. In children undergoing invasive procedures, the maximum stimulation would occur from the procedure itself. Titrating drugs to prevent patient response to these stimuli can result in a state of deep sedation or general anesthesia. However, the UMSS requires the repeated application of a uniform, quantifiable stimulus of the same intensity (e.g., rubbing the back and tickling the axillae) to assess response. Standardizing this stimulus is difficult and differing intensity of the stimulus may result in under- or over-estimating the level of sedation (15). This is another possible explanation of the wide standard deviation of the BIS values we observed at various UMSS sedation scores.

The BIS monitor, like other monitors including pulse oximetry, is not perfect and may be subject to artifact. EMG activity and transient BIS sensor dislodgement with vigorous patient movements, especially during invasive procedures with inadequate analgesia and sedation, may result in factiously high BIS values. It is therefore important not to rely solely on the BIS value demonstrated on the monitor but to correlate it with the clinical situation. When the bar graphs in the upper windows of the BIS monitor suggest that the signal quality is poor or that there is excessive EMG activity, the BIS values may not be accurate. However, the BIS monitor does provide useful objective information without the disadvantage of having to stimulate a patient regularly to establish the depth of sedation. BIS scores have been shown to be more accurate in reflecting the level of consciousness 60 seconds before the time of the recorded value (11). Stimulation can cause arousal and increase a previously low BIS value. We used an averaged BIS score over a 40-second period before application of the stimulus in our study. This may explain low BIS values at various clinically evaluated depths of sedation.

In previous studies on adult (20) and pediatric (14) populations, ketamine provided adequate sedation with high BIS values and there was a poor correlation of BIS scores with UMSS scores after the use of ketamine. We therefore purposely excluded children requiring sedation with ketamine in this study to avoid a confounding factor in the analysis. In our study there was no association between the BIS values and any specific sedative drug. In other studies, the effect of fentanyl on the BIS value was described as minimal, although its administration is associated with clinical evidence of increased sedation (21). In our study fentanyl was administered along with other drugs such as midazolam or pentobarbital and midazolam and so we cannot comment on the effect of fentanyl alone on the BIS values.

Age is another complicating issue in using BIS for assessing sedation in children, especially in infants <6 months of age, because the BIS algorithm was developed using adult EEG data. Brain maturation, synapse formation, and EEG changes with maturation continue after birth (22,23). The BIS algorithm based on adult EEG data may not correlate to all children, particularly infants. BIS scores in infants less than 6 months of age have been noted to be unreliable during general anesthesia (11). Denman et al. (12) had shown that BIS values in children undergoing surgery were inversely proportional to the end-tidal concentration of sevoflurane and there was a concentration-response difference between infants and older children. Davidson et al. (24) demonstrated a poor correlation between BIS and the depth of anesthesia in 23 infants. McDermott et al. (14) in their study showed that noncorrelating data pairs did not occur in any infants less than 6 months of age, but this correlation was analyzed in only six infants. Our study was limited to older children (>1 year) and hence we cannot comment on the validity of the BIS for measuring depth of sedation in infants.

Although this study suggests that there is a good correlation between BIS scores and the depth of sedation, it was not designed to provide data to support clinical benefits from titrating sedation to achieve a given BIS value. In adults undergoing monitored anesthesia care with propofol sedation, titrating sedation to achieve a BIS value has been associated with earlier awakening and shorter postanesthesia care unit stays. An important question still to be answered is whether titrating sedation to achieve a given BIS value in children is associated with greater therapeutic success in completing a procedure while avoiding the side effects of excessive sedation. In a recent study, sedation by standard protocols resulted in therapeutic failures because the goal of sedation was not achieved in 28% of children, whereas 8% of children experienced airway events and oxygen desaturation associated with deeper levels of sedation (25).

We conclude that the BIS monitor is an objective and nondisruptive tool for measuring depth of sedation in pediatric patients who were older than 1 year of age and who did not receive ketamine. Further investigations of the validity and clinical applicability of BIS assessment of sedation in a larger infant population should be pursued.

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