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Level of sedation evaluation with Cerebral State Index and A-Line Arx in children undergoing diagnostic procedures

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Summary

Background: Monitoring of anesthesia depth is difficult clinically, particularly in children. The aim of this study was to assess the correlation existing between CSI (Cerebral State Index), or AAI (A-line ARX) and a clinical sedation scale such as UMSS (University of Michigan Sedation Scale), during deep sedation with propofol in children undergoing diagnostic procedures.

Methods: Twenty ASA I and II children, scheduled to undergo deep sedation for magnetic resonance imaging (MRI) or Esophagogastro-duodenoscopy (EGDS), were enrolled. The patients were randomly assigned to receive depth of anesthesia monitoring with CSI or AAI. The anesthetist administered repeated doses of propofol every 10 s to a UMSS score of 3–4. An attending anesthetist, not involved in drug administration, recorded time and doses of sedation medications, vital signs, UMSS score and CSI or AAI score. All the evaluations were recorded at awake state (baseline), every 10 s until an UMSS score of 3–4 and every 3 min until the children were awake.

Results: We enrolled 13 males and seven females ranging in age from 8 months to 7 years. After induction of anesthesia CSI and AAI scores decreased and from the end of the procedure to emergence the two scores increased. The CSI data showed a strong correlation with the UMSS scores ($r = -0.861$; $P < 0.0001$); we found a similar correlation between the AAI data and the UMSS scores ($r = -0.823$; $P < 0.0001$).

Conclusions: Our study suggests that CSI and AAI may be two, real-time and objective tools to assess induction and emergence during propofol sedation in children undergoing EGDS and MRI.

Keywords: propofol; sedation; children; diagnostic procedures; cerebral state index; auditory evoked potential

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Introduction

Sedation is required in children for diagnostic procedures such as magnetic resonance imaging (MRI) and gastrointestinal endoscopy. Monitoring of anesthesia levels in the clinical setting is difficult, particularly in children. 'Conscious' sedation, deep sedation, or general anesthesia are a spectrum of pharmacologically induced depression of consciousness (1). Inadequate sedation or oversedation are common problems that may lead to movement, tachycardia and hypertension in the first case, respiratory depression, loss of airway reflexes and other cardiac and respiratory adverse events in the second. These adverse events, associated both with under- and oversedation, can be serious in the 'out-of-theater' setting, (2,3). An incorrect dosage is the commonest cause of excessive or inadequate depth of anesthesia particularly because of pharmacokinetics in children.

The assessment of anesthesia effect is crucial to ensure anesthesia is adequate. In clinical practice, a variety of responses are used to define the level of consciousness during diagnostic procedures in children. These include the Ramsay scale (RSS) and the University of Michigan sedation scale [UMSS; Table 1 (4,5)]. On close examination, the crucial measures within these scales are still very subjective. Lack of clear definition of consciousness makes it a difficult phenomenon to measure.

Advances in electroencephalogram (EEG) processing have produced new interest in measuring anesthesia effects. As a result several EEG-based anesthesia depth monitors have been produced. The Bispectral Index (BIS) is a useful tool to follow depth and delivery of sedation in adults who receive propofol, midazolam and volatile anesthetics (6). Although the BIS monitor was developed using EEG data acquired from healthy adults under general anesthesia, BIS also correlates with endtidal concentrations of some volatile anesthetic agents in children over 6 months of age (7–11). Previous studies have shown good correlation between the UMSS and BIS in a small number of children sedated with pentobarbital (5). However, recent data suggest that the BIS monitor does not correlate with the clinically derived RSS in children who were moderately or deeply sedated with pentobarbital and poor correlation in children sedated with chloral hydrate (12,13). Cerebral State index (CSI ^{TM}, Danmeter, Odense, Denmark) and A-line ARX (AAI ^{TM} Index; A-line AEP monitor, Danmeter A/S; Odense, Denmark) are two new monitors of anesthesia depth. Although these monitors have been extensively studied in adults, there are relatively few studies in children (14–17).

The aim of this randomized controlled study was to evaluate the correlation existing between CSI and AAI with the UMSS, during induction of propofol sedation and emergence, in children undergoing diagnostic procedures. If CSI and AAI are able to distinguish between light and deep sedation, then, theoretically, propofol could be titrated to a CSI and AAI score rather than the clinically derived UMSS. Titrating to a CSI and AAI score could reduce the dosage of propofol necessary and, potentially, provide a more precise and accurate method of dosing sedation to an objective endpoint.

Table 1
University of Michigan Sedation Scale (UMSS) (5)

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, rousable only with significant physical stimulation
4	Unarousable

Methods

After institutional informed written consent from the parents of patients and approval from Normal Institutional Office and Ethics Committee were obtained, 20 children, ASA I-II, fasted and premedicated, scheduled to undergo MRI or Esophagogastroduodenoscopy (EGDS) under sedation, were enrolled in the study protocol. Children were excluded in case of cognitive impairment, cerebral palsy or hypoxic brain injury.

All patients received EMLA cream placed on the expected site of the venepuncture and an oral premedication with midazolam (0.5 $mg \cdot kg^{-1}$, max. 7.5 mg) 20 min before the procedure. Monitoring consisting of a three-lead ECG, noninvasive blood

pressure and peripheral pulse oximetry. After standard monitoring a 22 G cannula was inserted and connected to a saline infusion. Parents were present until sedation was accomplished. Thereafter, children were randomly assigned to receive depth of anesthesia monitoring with CSI (group CSI) or AAI (group AAI) using a computer-generated random list.

The CSI score is passively derived from EEG signals and provides a numeric value scaled from 0 to 100. It uses an algorithm based on power analysis of beta, alpha and beta–alpha ratio with an estimation of burst suppression ratio. A CSI value >90 indicates awake, 71–90 conscious sedation, 61–70 deep sedation, 40–60 surgical anesthesia. (14,16). AAI is actively derived from EEG signal; the monitor delivers an auditory signal to the patient and tests the ability of brain to respond. The AAI provides a numeric value scaled from 0 to 60. In accordance with the manufacturer's instruction an AAI value of >50 indicates awake state, 25–50 light anesthesia, values between 15 and 25 indicates surgical anesthesia (15–17).

After preparation of the skin to reduce electrode impedance, CSI or AAI monitoring electrodes were positioned on the forehead and one on the mastoid process behind the ear, according to the manufacturer's instruction, and then connected to the CSM or AEP monitor. AAI also has two earphones to deliver acoustic stimuli.

Twenty minutes after preanesthesia with midazolam and 2 min after stabilization, baseline values were recorded. Thereafter, an attending anesthesiologist administered repeated doses of propofol 0.5 $mg{\cdot}kg^{-1}$ IV every 10 s until a UMSS score of 3 or 4 was achieved. After that the procedures started and in case of movement an extra dose of 1 $mg{\cdot}kg^{-1}$ of propofol was administrated to allow the conduct of the procedure. In all cases patients were maintained spontaneously breathing with no airway devices. Clinical characteristics of patients and propofol administration are presented in Table 2.

An anesthesiologist, not involved in drug administration, recorded doses of propofol, heart rate, oxygen saturation, UMSS score and CSI or AAI score. All the evaluations were recorded every 10 s from baseline until an UMSS score of 3–4 and every three minutes during the procedure and wake up until to an UMSS score of 0–1 (6). The assessment period was interrupted before entering the MRI room, starting again at the end of the examination when the patient was transferred to the recovery room. In the case of EGDS, the monitoring was not discontinued. All physicians involved in performing the diagnostic procedures and in administering sedation were blinded to CSI or AAI score.

Table 2
Clinical and surgical characteristics. Data are mean (±SD) or number of patients

	CSI (n = *10*)	*AAI* (n = *10*)
Age (years)	3 (2)	4 (2)
Weight (kg)	15 (4)	18 (10)
Female/male	3/7	6/4
EGDS/cephalic MNI	3/7	2/8
Propofol loading dose ($mg{\cdot}kg^{-1}$)	3.9 (0.3)	3.1 (0.7)
Total propofol dose ($mg{\cdot}kg^{-1}$)	4.1 (0.4)	3.5 (0.5)

The primary objective of the study was to evaluate a linear association between the CSI and AAI scores with the UMSS during induction of propofol sedation and emergence in children. Based on the two-sample Student *t*-test, seven patients with UMSS 3–4 provide over 90% power ($\alpha = 0{,}05$, $\beta = 0.10$) to detect a mean difference of 10 points in CSI and AAI assuming a standard deviation of 4 (effect size 1.0).

Weight and age of patients are presented as mean (±SD) and compared using a Student's *t*-test for unpaired samples. Variability of CSI and AAI values were calculated by coefficient of variation (CV). CSI and AAI values are presented as median and 10th–90th centiles and presented as scatter plots for each UMSS score.

Correlations were made between UMSS and CSI, AAI, using Spearman's correlation. We compared CSI and AAI values at different UMSS scores using Kruskall–Wallis with Dunn's Multiple Correlation test for non-parametric data. Statistical analyses were performed using the SPSS package (VERSION 13,0; SPSS, Chicago, IL, USA). Significance was defined as $P \leq 0.05$.

Results

Twenty children, 13 boys and seven girls, aged between 8 months and 7 years were enrolled. Ten patients were randomly assigned to group 'CSI' and ten to group 'AAI'. There were no significant differences in clinical characteristics, type of

diagnostic procedure or propofol loading dose between groups (Table 2). The mean duration of MRI was 26 min (11), while the mean duration of EGDS was 9 min (7).

After premedication, the baseline mean value of CSI and AAI were 93.8 (4.2) and 59 (2.0) respectively. At UMSS 3–4, the mean values were 54 (12) and 22 (7), respectively, for CSI and AAI. AAI showed a smaller baseline variability compared with CSI (coefficient of variation 3.38 for AAI vs 4.47 for CSI), while at UMSS 3–4 a larger variability for AAI (coefficient of variation 32.43 for AAI vs 23.71 for CSI) was observed. The smaller coefficient of variation of AAI than CSI can be considered a statistical demonstration of a better ability of the first monitor to capture the transition from awake to sedation state; similarly the smaller coefficient of variation of CSI than AAI when the patients were sedated demonstrates the better ability of CSI to distinguish deeper states of anesthesia. Moreover, there was a clinical correspondence for this statistical significance.

Repeated doses of propofol produced a significant decrease in CSI and AAI values until UMSS 3–4 was reached ($P < 0.001$). Comparison between all the AAI and CSI values at baseline (UMSS = 0–1) vs all the values at UMSS = 3–4 was performed using Dunn's multiple comparison test. The statistical analysis showed a significant difference from baseline (UMSS 0–1) to UMSS 3–4 values in both groups ($P < 0.001$). This suggests that the two monitors are able to distinguish light (UMSS 0–1) from deep sedation (UMSS 3–4).

CSI and AAI scores increased from the end of the procedure to emergence. CSI and AAI data showed a strong correlation with the UMSS scores (CSI $r = -0.861$; $P < 0.0001$. AAI $r = -0.823$; $P < 0.0001$; Table 3); we found a similar correlation between the AAI data and the UMSS scores (Figures 1 and 2). Figure 3 shows the AAI and CSI values, respectively, for each patient of the two groups from begin of sedation until wake up.

There was no evidence of statistical significance between CSI score and vital signs such as [heart rate (HR), while a weak correlation was found between AAI and HR ($P < 0.05$); Figure 4]. Otherwise, no evidence of statistical correlation was found between HR and UMSS in all patients of the two groups. This is an interesting concept useful for future research in patients undergoing sedation or general anesthesia.

Table 3
Spearman correlation coefficient (r) and P-value for CSI and AAI with UMSS and HR. The CSI data showed a strong correlation with the UMSS scores. A similar correlation was found between the AAI data and the UMSS scores. There was no evidence of statistical significance between CSI score and HR, while a weak correlation was found between AAI and HR

	UMSS		*HR*	
	r	P-*value*	*r*	P-*value*
CSI	−0.8619	<0.0001	0.0039	NS
AAI	−0.8237	<0.0001	0.2382	<0.05

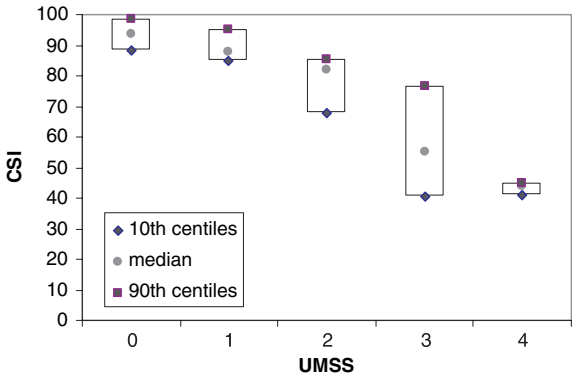

Figure 1
CSI during different sedation level. Repeated doses of propofol produced an increase in sedation (UMSS 0–4) associated with a gradual decrease in CSI values. To show the scatter of the data 10th centiles, median and 90th centiles are presented. The P-value was <0.0001.

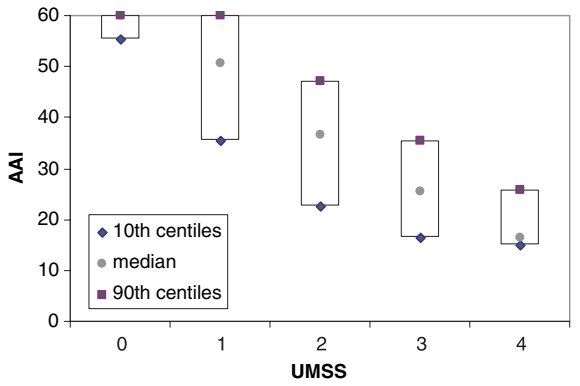

Figure 2
AAI during different sedation level. Repeated doses of propofol produced an increase in sedation (UMSS 0–4) associated with a gradual decrease in AAI values. To show the scatter of the data 10th centiles, median and 90th centiles are presented. The P-value was <0.0001.

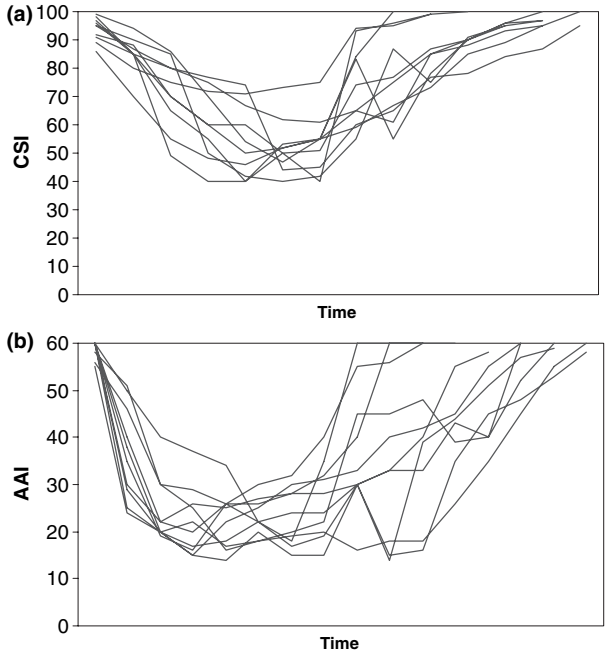

Figure 3
CSI (a) and AAI (b) scores in the two group, starting from baseline value until wake up. Each line represent a patient.

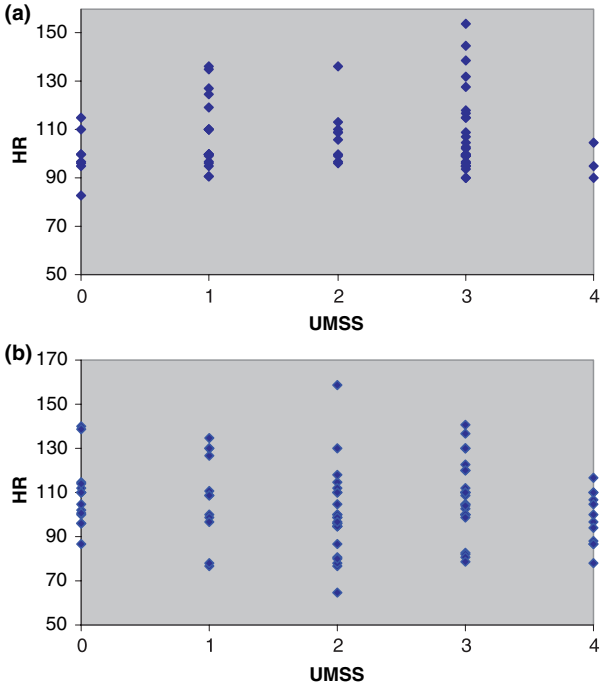

Figure 4
Distribution of HR in different level of sedation. No statistical correlation between HR and CSI (a) or HR and AAI (b) was found.

There were no major adverse events, but a 4-year-old patient receiving a propofol loading dose of 3.5 $mg \cdot kg^{-1}$ until the achievement of an UMSS of 4, developed apnea, which required bag-ventilation via facemask and showed an AAI score of 16.

Discussion

We performed a prospective study comparing two new anesthesia depth monitors with a validated sedation scale, during induction and emergence from propofol sedation in children. We supported the hypothesis that if CSI and AAI are able to distinguish between light and deep sedation, then, theoretically, propofol could be titrated to a CSI and AAI score rather than the clinically derived UMSS. Our results showed a significant correlation between AAI and CSI and UMSS.

The depth of anesthesia followed the predictable order of physiological changes seen as the dose increased. However, 'measuring' anesthesia is not as simple as it seems. In the clinical setting, we routinely use vital signs, the ability of patients to respond to verbal or painful stimuli and titration of medications to achieve the desired level of sedation. A variety of approaches based on experience, technology and location have been described to measure depth of sedation in children (6,18,19).

The clinical measurement of depth of anesthesia was performed through the UMSS, a simple observational five-point scale. Malviya *et al*. (5) tested the validity and reliability of UMSS in children aged 4 months–5 year undergoing sedation for computer tomography (CT). The UMSS was compared with a visual analogue scale (VAS) and the Observer's Assessment of Alertness/Sedation Scale (OAAS) and the authors concluded that the UMSS is a simple and valid tool in the documentation of depth of sedation in children. The UMSS has been applied in several clinical trials which compared number-scaled sedation scores, such as BIS, with clinical evaluation of depth of sedation (13,20).

To best of our knowledge, this is the first report that looks at the relationship between AAI, CSI, and UMSS in children. In essence, there are two ways to use these devices in the clinical setting. First, as a machine that quantifies a component of anesthesia, and secondly, as a guide or arbitrary scale, to guide the anesthetist through anesthesia using particular

drugs. Both machines have been compared with the bispectral index (BIS) and clinical sedation scales, in an adult population (17,21). Further studies are needed to evaluate the AAI and CSI capabilities to prevent adverse effects, discomfort for patients and also to shorten the discharge time (18,19,22,23).

The relationship between EEG and consciousness is indirect. Information from EEG derived anesthesia depth monitors is determined in part by both arousal and by direct effects of anesthetic agents. The association between EEG derived anesthesia depth monitors and arousal, and the indirect association between EEG derived anesthesia depth monitors and consciousness remains valid only if the relative actions of the anesthetic drugs on the EEG, arousal and consciousness are consistent and reproducible. This is the case for isoflurane, propofol, thiopentone, and midazolam (24,25). In this study, propofol induction resulted in a progressive and significant decrease in CSI and AAI values from baseline to UMSS scale values of 3–4. CSI has a better ability to capture the transition from light to deep sedation. CSI showed less interpatient variability than AAI at UMSS 3–4. The variability of AAI scores in this study indicates that, for different patients, the AAI values can have a very wide range of values. In some instances, AAI assigns deeply sedated children numerical values which many would consider to be a state of wakefulness (AAI values: 50–60).

There are some limitations to our study. Monitoring is not possible in the MRI suite because the AAI and CSI monitors and sensor probes are not compatible with the magnetic resonance environment, so the two monitors were disconnected from the patients during the performance of the imaging. This was a limitation; however, the aim of our study was the evaluation of patients during induction and emergence from anesthesia. The UMSS is a clinically derived scoring system, which implies a possible subjective error in differentiating between levels 3 and 4. As for other clinical sedation scales, it requires noxious physical stimulation to distinguish level 4 from level 3. We did not intend to make any difference between UMSS 3 and 4 because it could be counterproductive and interfere with the diagnostic study. The small sample size associated with a broad age spectrum may represents a confounding factor. The changes seen in the EEG with maturation, make it very difficult to presume that the correlation between EEG, arousal and anesthesia, which is quite likely in adults is equally likely in children. The uncertainty increases as age decreases. Finally, both monitors have not been applied on the same patient because they work in an opposite way: CSI is passively derived from EEG, while AAI is actively derived from EEG, thus auditory stimuli of AAI could affect the CSI index. Moreover, it was not easy to place the electrodes for both monitors on the forehead of a small patient (26–28).

In conclusion, our study suggests that CSI and AAI may be two, real-time and objective tools to assess induction and emergence during propofol sedation in children undergoing EGDS and MRI.

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