

Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block

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Background. The bispectral index (BIS) and the rapidly extracted auditory evoked potentials index (A-line ARX Index or AAI) have been proposed as methods to measure the depth of sedation. A prospective study was designed to assess the performance of both these methods for measuring the depth of sedation induced by propofol or midazolam under epidural block.

Methods. Thirty-two ASA I and II adult patients undergoing elective gynaecological surgery under low-thoracolumbar epidural block were studied. Eighteen patients received propofol (Group P: 20 mg bolus every 3 min) and 14 received midazolam (Group M: 0.5 mg bolus every 5 min) until an observer's assessment of alertness/sedation (OAA/S) scale score of I was achieved. AAI and BIS were monitored for different OAA/S scores.

Results. AAI and BIS decreased and increased following the changes on the patients' OAA/S scores and correlated with sedation significantly. During the onset phase, the coefficients of Spearman's rank correlation for AAI and BIS were respectively 0.958 and 0.898 ($P < 0.001$) for Group P, and 0.973 and 0.945 ($P < 0.001$) for Group M. During the recovery phase in Group P, the coefficients were respectively 0.946 and 0.702 ($P < 0.001$). Linear regression analysis showed that both AAI and BIS were linearly related to the OAA/S scores. The coefficients of Spearman's rank correlation and linear regression for AAI were all greater than those for BIS ($P < 0.05$).

Conclusions. Both AAI and BIS correlated well with the depth of sedation induced by propofol or midazolam under epidural block. AAI may be more valuable when monitoring depth of sedation.

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Many studies have reported that the bispectral index (BIS) reflects depth of anaesthesia much better than other techniques. It correlates well with the blood concentration of many anaesthetic drugs and the depth of sedation.^{1–3} Recently, a great deal of attention has been paid to the assessment of the depth of anaesthesia by analysis of auditory evoked potentials (AEP).^{4–6} A non-invasive sedation/anaesthesia monitor based on AEP analysis, the A-line (Danmeter A/S, Odense, Denmark) has been developed recently. It monitors depth of anaesthesia by extraction of mid-latency AEP (MLAEP) and presents the results by means of the A-line ARX Index (AAI).

In this study, we analysed the changes in AAI and BIS during sedation induced by propofol or midazolam under low-thoracolumbar epidural block.

Methods

After institutional ethics committee approval, informed consent was obtained from 32 female patients (ASA I and II) scheduled for elective gynaecological surgery under low-thoracolumbar epidural anaesthesia. Patients with psychiatric disorders or hearing abnormalities were excluded from the study.

The patients were divided into two groups, 18 in the propofol group (Group P) and 14 in the midazolam group (Group M). In Group P, they ranged in age from 38 to 64 yr with a mean of 47.9 (SD 7.7) yr, and in weight from 48 to 72.5 kg with a mean of 59.3 (5.3) kg, while in Group M they ranged in age from 25 to 60 yr with a mean of 43.2 (8.8) yr and in weight from 42.5 to 72 yr with a mean of 58.8 (8.9) kg.

Table 1 Observer's assessment of alertness/sedation (OAA/S) scale

Responsiveness	Speech	Facial expression	Eyes	Composite score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking				1

Patients were not premedicated and were fasted for at least 8 h. After they had rested for 10 min in the operating room, AAI, BIS, arterial pressure, heart rate (HR) and SpO₂ monitoring was commenced. In order to minimize artefacts, patients were asked to close their eyes.

Epidural puncture was performed through vertebral interspace L1–2 for surgery on the uterine appendages or hysteromyomectomy, or T12–L1 and L3–4 for hysterectomy. A mixture of 1.6% lidocaine, 0.2% tetracaine and 1:200 000 epinephrine, was administered in increments of 3–5 ml every 5 min until satisfactory blockade was achieved. All patients received supplemental oxygen (3–4 litres min⁻¹) via nasal cannula and an experienced anaesthetist monitored respiratory and cardiovascular function and determined the need for interventions such as jaw support to maintain an adequate airway or a tight-fitting face mask to supply oxygen.

When surgery commenced on the uterus or uterine appendages, an i.v. bolus dose of propofol 20 mg every 3 min was given to patients in Group P or midazolam 0.5 mg every 5 min in Group M until an observer's assessment of alertness/sedation (OAA/S) scale⁷ score of 1 was achieved (Table 1). The OAA/S scores were assessed by one blinded investigator. AAI and BIS values were recorded at different OAA/S scores during the onset and recovery phases.

AAI was monitored using the A-line monitor (Danmeter A/S). MLAEP were elicited with a bilateral click stimulus of 70 dB intensity and 2 ms duration. Three neurological electrodes (Neuroline, 720-00-S, Medicotest A/S, Denmark) were positioned at mid-forehead (positive), left forehead (reference) and left mastoid (negative) to obtain the EEG signals. The AEP analysis window has an 80 ms duration and preprocessing of the EEG sweeps consisted of artefact rejection and 16–150 Hz infinite impulse response Butterworth digital band-pass filtering. An ARX modelling process is then applied in order to facilitate rapid extraction of the AEP.

BIS, arterial pressure, HR and SpO₂ were monitored using the HXD-1 series block-type multifunctional monitor (Huaxiang, Heilongjiang, China). BIS was continuously

calculated from two bipolar electroencephalographic channels using five silver–silver chloride electrodes (Meditrace, Ludlow com., Canada) applied to the scalp (Fp1–F7, Fp2–F8, international 10–20 system, with one placed at the midline near mid-forehead as the reference). The update time was 2.5 s.

BIS and AEP machines have sophisticated artefact rejection algorithms, and the auditory clicks generate signals 100 times smaller than the remainder of the EEG, so there is no interference between the two machines that could affect the data when they are used simultaneously.

Statistical analysis of the results was performed by means of Spearman's rank correlation analysis, linear regression analysis and one-way ANOVA using SPSS software 10.0 (SPSS Inc., Chicago, IL, USA). Probability values <0.05 were considered statistically significant.

Results

Epidural blockade was adequate for all patients. The total dose of local anaesthetics used before the administration of propofol or midazolam ranged from 7 to 20 ml with a mean of 12.3 (3.2) ml in Group P, and from 9 to 18 ml with a mean of 12.7 (3.0) ml in Group M. AAI and BIS values after epidural blockade did not differ from those before blockade.

Group P originally consisted of 22 patients. After several bolus doses of propofol, symptoms including restlessness, excitement and hallucinations occurred in four patients, and both AAI and BIS increased to >90. They were excluded from the study. Of the other 18 patients, sedation deepened and the OAA/S scores decreased following propofol administration. The total dose of propofol administered to obtain an OAA/S score of 1 was 108.9 (45.1) mg. AAI and BIS decreased as sedation deepened, and increased progressively to the baseline as sedation lightened. AAI and BIS showed a significant correlation with the OAA/S scores. During the onset phase, the coefficients of Spearman's rank correlation were respectively 0.958 and 0.898 ($P<0.001$). During the recovery phase, the coefficients were 0.946 and 0.702 ($P<0.001$) (Table 2).

Table 2 Mean (SD) AAI and BIS values during the onset and recovery phases of the sedation induced by propofol or midazolam. r =the coefficients of Spearman's rank correlation; ** $P<0.01$, the probability values of the correlation of AAI or BIS with the OAA/S scores. Using one-way ANOVA, AAI values show significant differences between any two OAA/S scores during the onset or recovery phases in the two groups. BIS values show significant differences between any two scores during the onset or recovery phases in Group M and differ significantly between any two scores except 2 and 3 during the onset phase, and between 5 and any one of 2, 3 or 4 during the recovery phase in Group P.

OAA/S score	AAI		BIS	
	Group P	Group M	Group P	Group M
<i>Onset</i>				
5	84.3 (7.2)	87.1 (5.9)	95.0 (2.1)	95.5 (1.1)
4	70.2 (9.0)	68.5 (6.3)	91.9 (2.0)	91.4 (1.7)
3	46.0 (10.5)	42.2 (6.8)	84.7 (5.8)	79.1 (11.3)
2	28.2 (7.3)	28.1 (4.2)	80.3 (8.0)	63.9 (9.6)
1	17.3 (2.4)	17.7 (2.1)	69.9 (8.9)	48.4 (6.4)
r	0.958**	0.973**	0.898**	0.945**
<i>Recovery</i>				
2	28.4 (6.8)	30.0 (7.5)	83.2 (9.4)	52.3 (6.6)
3	44.7 (8.3)		87.6 (6.7)	
4	69.1 (6.6)		90.3 (5.6)	
5	82.3 (6.0)	73.2 (5.7)	94.5 (2.4)	91.9 (2.5)
r	0.946**		0.702**	

In Group M, sedation deepened and the OAA/S scores decreased following the administration of midazolam. The total dose of midazolam administered before achieving an OAA/S score of 1 was 5.0 (1.3) mg. During the onset phase, both AAI and BIS decreased as the patient's OAA/S scores decreased, showing significant correlation with the depth of sedation. The coefficients of Spearman's rank correlation were respectively 0.973 and 0.945 ($P<0.001$) for AAI and BIS (Table 2). During the recovery phase, when patients responded to mild prodding (OAA/S scores 2), AAI was 30.0 (7.5) and BIS 52.3 (6.6). All patients then awoke abruptly, (reaching an OAA/S score of 4–5), and AAI and BIS increased rapidly to 73.2 (5.7) and 91.9 (2.5), respectively, although BIS changed a little more slowly for 30–60 s. During the next 30 min, OAA/S scores remained at 4–5 and BIS at approximately 90, whereas AAI fluctuated to some extent (55–99).

Linear regression analysis showed that both AAI and BIS were linearly related to the OAA/S scores (Fig. 1 and Fig. 2). The coefficients of Spearman's rank correlation and linear regression for AAI all differed significantly from the corresponding ones for BIS ($P<0.05$).

Using one-way ANOVA, AAI values showed significant differences between any two OAA/S scores during the onset or recovery phases in the two groups. BIS values differed significantly between any two scores during the onset or recovery phases in Group M, and differed significantly between any two scores except 2 and 3 during the onset phase, and between 5 and any one of 2, 3 or 4 during the recovery phase in Group P.

As shown in Figure 1 and Figure 2, some AAI and BIS values recorded at one OAA/S score were within the range of values at another score, especially the adjacent score.

Discussion

BIS combines information on the frequency, power, and harmonic and phase relationships between the component waves of the EEG. It is the first method specifically approved by the FDA for measurement of the hypnotic effects of drugs.¹ In a previous study by the present authors, BIS showed good correlation with the depth of midazolam-induced sedation.⁸ Also, Liu, Singh and White⁹ found that BIS exhibited the best correlation with OAA/S scores during both the onset ($r=0.815$) and recovery ($r=0.596$) phases of midazolam-induced sedation of all the EEG parameters studied. The same authors showed that BIS also exhibited a better correlation with the OAA/S scores during both the onset ($r=0.744$) and recovery ($r=0.705$) phases of propofol-induced sedation.¹⁰ Glass and colleagues¹¹ have reported that BIS correlated with the OAA/S scores significantly better than the measured propofol concentration ($r=0.883$ vs $r=-0.778$, $P<0.05$). It also correlated as effectively as the measured concentration for midazolam and isoflurane.

A great deal of attention has recently been paid to the analysis of AEP for monitoring depth of anaesthesia. In particular, MLAEP are thought to have anatomical significance and to provide a good indication of the responsiveness of the CNS.^{4–6} Many previous studies have shown that MLAEP amplitudes and latencies changed with many anaesthetics in a dose-dependent manner, making the analysis of MLAEP a promising way for measuring depth of anaesthesia.^{1 2 5 6 12 13}

Typically, AEP were measured and displayed as amplitudes and latencies off-line. Then a quantitative measure of changes in AEP, the AEP index (AEP_{index}) was proposed.¹⁴ There are two identification models to

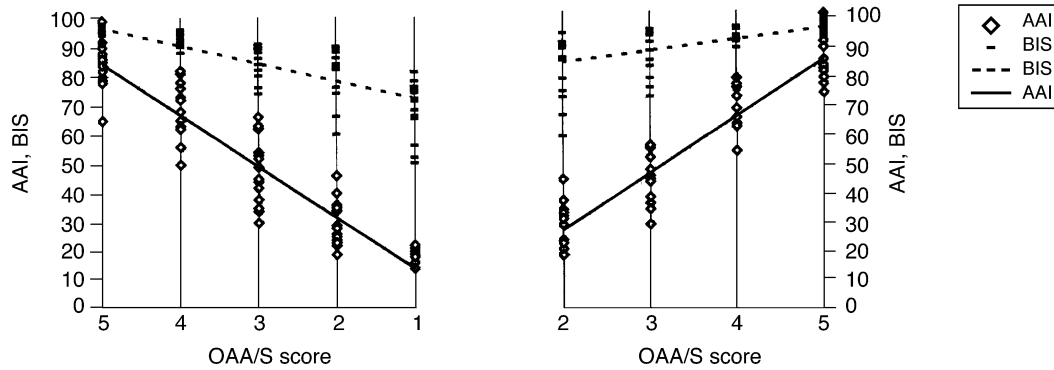


Fig 1 Scatterplot showing individual AAI and BIS at different OAA/S scores during the onset and recovery phases of propofol-induced sedation. The linear regression lines were analysed. $AAI=17.60(OAA/S \text{ score})-3.62$; $BIS=6.18(OAA/S \text{ score})+65.83$; $n=90$, during the onset phase. $AAI=18.61(OAA/S \text{ score})-8.97$; $BIS=3.68(OAA/S \text{ score})+76.02$; $n=72$, during the recovery phase.

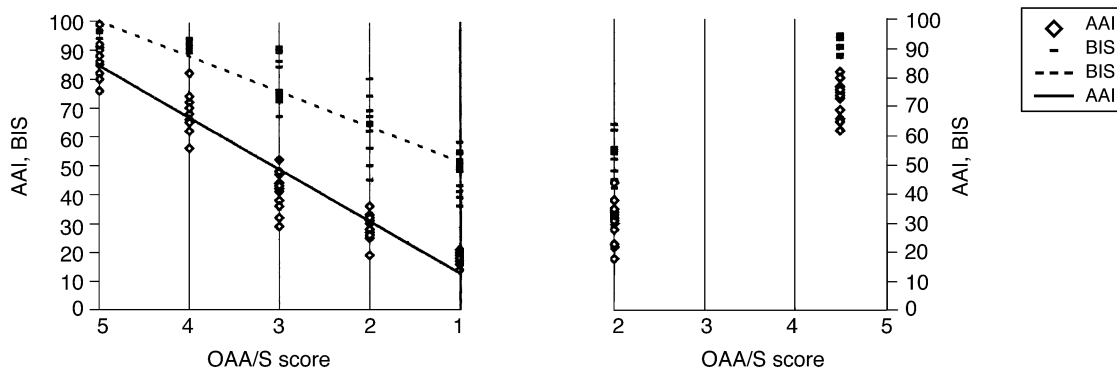


Fig 2 Scatterplot showing individual AAI and BIS at different OAA/S scores during the onset and recovery phases of midazolam-induced sedation. The linear regression lines were analysed. $AAI=17.91(OAA/S \text{ score})-5.03$; $BIS=12.25(OAA/S \text{ score})+38.96$; $n=70$, during the onset phase.

evaluate the $MLAEP_{index}$: the moving time average model (MTA model) and the autoregressive model with exogenous input (ARX model). The MTA model needs an average of 256 sweeps that lasts approximately 45 s, whereas the ARX model enables extraction within 15–25 sweeps, needing only 2–6 s.^{5 6 15} Many studies have reported that the ARX-model extracted $MLAEP_{index}$ changed significantly during anaesthesia induced with thiopental, propofol, isoflurane and desflurane.^{5 6 15 16} This ARX model has been applied to the A-line monitor to facilitate rapid extraction of the $MLAEP$ (20–80 ms) and on-line monitoring of the depth of sedation with the AAI.

In this study, AAI and BIS decreased and increased following changes in OAA/S scores and correlated well with the depth of sedation. Linear regression analysis showed that both AAI and BIS were linearly related to the OAA/S scores. However, the coefficients of Spearman's rank correlation and linear regression for AAI were all greater than the corresponding ones for BIS. AAI values differed significantly between any two OAA/S scores during both the onset and recovery phases in the two groups, while BIS values did not differ significantly between the scores 2

and 3 during the onset phase, or between any two of the scores 2, 3 and 4 during the recovery phase in Group P. These results imply that AAI is more valuable.

There was a substantial overlap of the ranges of AAI, and also of BIS, at some levels of sedation. This reveals the same problem of sensitivity and specificity for AAI and BIS that has been apparent with other methods of measuring the depth of sedation. However, since we still lack a satisfactory method of monitoring sedation, AAI and BIS can be used to provide useful trend information in the individual patient.

In summary, both AAI and BIS correlated well with the depth of sedation induced by propofol or midazolam under epidural block. AAI may be more valuable when monitoring the depth of sedation.

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