The Correlation Between Bispectral Index and Observational Sedation Scale in Volunteers Sedated with Dexmedetomidine and Propofol

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BACKGROUND: Bispectral index (BIS) is a widely used quantitative parameter for evaluating anesthesia and sedation levels. Dexmedetomidine is a novel sedative, providing sedation while patients remain cooperative and can be easily aroused; as a consequence, BIS used with dexmedetomidine may poorly characterize sedation. Thus, we tested the hypothesis that BIS values are lower with dexmedetomidine than with propofol at comparable Observer’s Assessment of Alertness and Sedation (OAA/S) scores.

METHODS: This was a randomized, 2-day, crossover study. On the first study day, healthy volunteers were randomly allocated to either propofol or dexmedetomidine sedation. Drugs were administered using computer-controlled infusions targeting an effect-site concentration of 1, 2, and 4 μg/mL for propofol or a plasma concentration of 0.6, 1.2, and 2.4 ng/mL for dexmedetomidine. The relationship between BIS and OAA/S score was obtained 20 and 40 min after changing each drug concentration. BIS values at each OAA/S score were compared between drugs. The cutoff values of BIS for OAA/S score of ≤2 were obtained by analysis of receiver operating characteristic curves.

RESULTS: Nine volunteers were included in our analysis. Heart rates decreased significantly with dexmedetomidine sedation. ETco₂ was significantly increased with high doses of propofol but did not increase with high doses of dexmedetomidine. BIS values at OAA/S scores of 1, 2, 3, 4, and 5 during propofol sedation were 95.5 (90–97), 78 (71–84.5), 67 (64–70), 57 (51.5–60), and 34 (30–37), respectively. BIS values at OAA/S scores of 1, 2, 3, 4, and 5 during dexmedetomidine sedation were 95 (79–98), 62 (53.5–68.5), 45.5 (45.3–52), 39.5 (34.3–41.8), and 24.5 (22.5–30.5), respectively. BIS values were significantly less with dexmedetomidine than propofol at OAA/S responsiveness scores of 2, 3, and 4. The calculated cutoff BIS values for OAA/S scores of ≤2 were 67 (sensitivity of 86%, specificity of 97%, and area under the curve of 0.98) for propofol and 46 (sensitivity of 84%, specificity of 91%, and area under the curve of 0.96) for dexmedetomidine.

CONCLUSION: The combination of both BIS and sedative scales could provide different and complementary data to the clinician evaluating the patient’s response to sedation than would either tool alone, especially when dexmedetomidine is used.

Proper assessment of the sedation status is important for the management of patients in operating rooms, critical care units, and during invasive procedures. The Observer’s Assessment of Alertness and Sedation (OAA/S) score is a well-established evaluation of several sedative drugs. However, the OAA/S score requires clinician interaction with subjects and thus risks “waking” them. The bispectral index (BIS) is a continuous noninvasive electroencephalographic (EEG) method that has been proposed to monitor the hypnotic state during sedation and anesthesia. For propofol, the correlation between BIS and drug concentration is well documented. Dexmedetomidine is a highly selective central α2-adrenergic receptor agonist with specific sedative properties, including arousable sedation, analgesia sparing, and little respiratory depression. Furthermore, patients sedated with dexmedetomidine remain cooperative and can be easily aroused for procedures and clinical testing. However, a consequence is that conventional sedation scoring systems based on clinical observations may not work well for dexmedetomidine-induced sedation. There is a precedent for this concern because there is a divergence...
between EEG measures and clinical scoring of sedation for several other drugs.1,2,8 Thus, we tested the hypothesis that BIS values are less with dexmedetomidine than with propofol sedation at comparable OAA/S scores.

**METHODS**

The study was conducted at the University of Louisville with university approval (including Health Insurance Portability and Accountability Act and conflict-of-interest regulations), IRB approval, approval from University Hospital, and written informed consent from the participating volunteers. The study was conducted under Good Clinical Practice guidelines. Volunteers were recruited by advertisements in the local newspapers, flyers posted at the local universities, and other measures.

**Subject Selection**

Eleven healthy volunteers aged 18–40 yr were enrolled in the study but only 9 completed both days. All subjects had a detailed prestudy examination. Volunteer exclusion criteria included obesity with a body mass index >30 kg/m², pregnancy, and drug or alcohol abuse. The volunteers took no chronic medications including anticonvulsants, antidepressants, or other psychoactive medications. Before each study day, subjects fasted after midnight.

**Protocol**

We used a randomized, 2-day crossover study design. On arrival on the first study day, volunteers were allocated to propofol or dexmedetomidine sedation according to a computer-generated randomization. Treatment allocations were maintained in sequentially numbered opaque envelopes. On the subsequent study day, at least 7 days after the initial study day, the alternate drug was used. Study drugs were prepared by independent investigators, and assignments were blinded for the subjects.

Propofol and dexmedetomidine were given via target-controlled infusion (TCI) using a Harvard infusion pump (Harvard Clinical Technology, South Natick, MA) driven by STANPUMP software using a ke0 value of 0.456/min (available at http://www.opentci.org/doku.php).6 This TCI system is designed for research use and not approved for clinical purposes in United States.

The propofol pharmacokinetic parameters were obtained from Schnider et al.,9 and height-adjusted dexmedetomidine pharmacokinetic parameters were applied.10 Propofol was administrated in increasing steps to target effect-site concentrations of 1, 2, and 4 \( \mu g/mL \); dexmedetomidine was given to target plasma concentrations of 0.6, 1.2, and 2.4 ng/mL. Each concentration was maintained for 40 min. Each volunteer was given 2 L/min supplemental oxygen through a nasal cannula.

**Measurements**

Electrocardiogram, heart rate, noninvasive systolic and diastolic arterial blood pressures, \( \text{Sp}_2 \), and BIS (BIS XP 3.4 monitor, Aspect Medical Systems, Newton, MA) were monitored. Side-stream nasal cannulae were used for the measurement and were analyzed by gas monitor (Datex-Engstrom, Helsinki, Finland). The 5-point scale OAA/S score was used to record the responsiveness subcomponents (Table 1).1 Sedation was evaluated using OAA/S score at 20 and 40 min for each drug concentration; in each case, BIS was recorded before each OAA/S evaluation.

**Statistical Analysis**

The sample size was calculated with approximately 80% power to detect sedative group differences in mean BIS values of \( \geq 15 \) (assuming a between-subjects SD of 10 and a within-subject correlation coefficient of 0.6 for the repeated measures).

BIS and OAA/S score combinations were used for analysis obtained once just before starting drug infusion and twice (at 20 and 40 min) after changing each target concentration (low, middle, and high dose). Thus, 7 BIS and OAA/S pairs were included in the analysis from each subject for each study drug.

SPSS version 16.0 (SPSS, Chicago, IL) for Windows was used for statistical analysis, with values expressed as mean \( \pm \) SD whenever appropriate. One-way repeated analysis of variance was applied for evaluating

<table>
<thead>
<tr>
<th>Subscore</th>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Does not respond to mild prodding or shaking</td>
<td>Few recognized words</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is spoken loudly and/or repeatedly</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis</td>
</tr>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
</tr>
</tbody>
</table>

The final score is the sum of the Responsiveness, Speech, Facial expression, and Eyes component scores. Thus, a "wide awake" score \( = 5 \) and a deeply sedated score \( = 1 \).
the dose dependency of the hemodynamic parameters, Spo2, and ETco2. Two-factor, repeated-measures analysis of variance and appropriate post hoc analysis were applied to compared BIS values using dexmedetomidine versus propofol as the between-subject factor and the OAA/S score as the within-subject factor (for modeling purposes, equal spacing between the levels of OAA/S was assumed). To obtain the cutoff BIS value that estimates a hypnotic status, receiver operating characteristic curve analysis was used to evaluate the BIS score that provides the optimal combination of sensitivity and specificity for predicting an OAA/S score of 2 with each sedative. A P value <0.05 was considered statistically significant.

RESULTS
Eleven volunteers started the study. For personal reasons, 2 volunteers withdrew after the first study day. The remaining 9 volunteers (3 women and 6 men), aged 24 ± 4 yr, body weight of 70 ± 13 kg, and height of 176 ± 6 cm completed the study and were included in the analysis.

Hemodynamic variables are shown in Figure 1. All subjects maintained spontaneous breathing

Figure 1. Noninvasive arterial blood pressure, heart rate, Spo2 with 2 L/min oxygen via nasal cannula, and ETco2. BP = systolic blood pressure; BPd = diastolic blood pressure; HR = heart rate; and ETco2 = end-tidal co2, which was obtained from the nasal cannulae. Data are shown with mean and 95% confidence interval as well as individual plots. *P < 0.05, **P < 0.01.
throughout the study. Heart rate decreased significantly during dexmedetomidine administration. Although ETCO\textsubscript{2} was significantly increased with high doses of propofol, ETCO\textsubscript{2} remained normal even with high doses of dexmedetomidine.

The relationship between OAA/S score and BIS is shown in Figure 2. BIS values at OAA/S scores of 1, 2, 3, 4, and 5 during propofol sedation were 95.5 (90–97), 78 (71–84.5), 67 (64–70), 57 (51.5–60), and 34 (30–37), respectively. BIS values at OAA/S scores of 1, 2, 3, 4, and 5 during dexmedetomidine sedation were 95 (79–98), 62 (53.5–68.5), 45.5 (45.3–52), 39.5 (34.3–41.8), and 24.5 (22.5–30.5), respectively. BIS was significantly lower with dexmedetomidine than with propofol at OAA/S responsiveness levels of 2, 3, and 5.

Receiver operating characteristic analysis identified BIS values with the best level of discrimination to obtain an OAA/S score of 2 of 5 during dexmedetomidine and propofol administration. The calculated cutoff BIS value for propofol sedation was 67 (sensitivity of 86%, specificity of 97%, and area under the curve of 0.98); the analogous BIS value for dexmedetomidine was 46 (sensitivity of 84%, specificity of 91%, and area under the curve of 0.96; Fig. 3).

**DISCUSSION**

BIS is an empirically derived multifactorial EEG parameter that relies on the correlation of the phases between frequency components of the EEG. BIS reports the hypnotic state as a value between 0 and 100. However, BIS values do depend on the specific sedative. For example, ketamine paradoxically increases BIS despite a deep clinical level of hypnosis.\textsuperscript{2,11} Clonidine, an \(\alpha_2\) receptor agonist, which has similar pharmacological features to dexmedetomidine, decreases BIS.\textsuperscript{12} It also increases \(\delta\) EEG activity and decreases \(\alpha\) activity over the parieto-occipital region.\textsuperscript{13}

The OAA/S score also has potential disadvantages. For example, obtaining a score generally requires some extrinsic patient stimulation such as calling, prodding, or shaking to evaluate the subject’s neurological status. The assessment itself can therefore affect the sedative status if sedation is not deep. Clinical scoring systems are not applicable for deeply sedated or relaxed patients, and results are dependent on the assessor. Observational sedation scales indicate a patient’s status at a single moment in time and require the assessor to rate the level of sedation on the basis of a single period of observation and interaction with the patient. Discrete observations thus fail to account for changes in sedation level that may occur between assessments.

Our main finding is that at comparable OAA/S scores, BIS values were lower with dexmedetomidine sedation than with propofol. It is widely recognized among anesthesiologists that BIS values between 40 and 60 generally indicate adequate general anesthesia.
for surgery and improve recovery.14 During dexmedetomidine sedation, however, 85% of the BIS values were between 40 and 60 when the OAA/S responsiveness was 3, which is considered an arousable and shallow sedation level. Our results thus indicate that the calibration for BIS differs with dexmedetomidine and propofol, and clinicians should interpret BIS values in light of the drugs being used.

It is important to note that the characteristics of dexmedetomidine sedation differ markedly from other sedatives, including propofol. Hyperpolarization of noradrenergic locus ceruleus neurons seems to be an important factor for sedative activity of dexmedetomidine.15,16 The transcriptional activator c-Fos expression pattern is similar to endogenous nonrapid eye movement sleep under sedation by dexmedetomidine, which is not the case when sedation is induced by GABAergic agonists.15,17 Overall, dexmedetomidine enhances the nonrapid eye movement sleep-promoting pathways, mainly at locus caeruleus.

Arousable sedation when using dexmedetomidine seems to be preferred in certain patients (i.e., lack of respiratory depression and easy awakening), but makes it difficult to directly compare sedation with dexmedetomidine and propofol even when using a single sedation scoring system. Therefore, low BIS values at any given OAA/S score do not indicate that BIS is “wrong,” rather that the characteristics of the 2 drugs differ substantially and that BIS values need to be interpreted in context.

OAA/S scores and BIS values assess different domains relating to sedation. Similarly, Turkmen et al.18 found significant correlation ($r = 0.9; P = 0.0001$) between Richmond Agitation and Sedation scale and BIS during dexmedetomidine sedation in critically ill patients. The Richmond Agitation and Sedation scale is designed to assess mechanically ventilated patients and therefore not only evaluates alertness but also agitation. The combination of both tools could provide different and complementary data that will ensure a greater understanding of the patient’s response to sedation than would either tool alone, especially when dexmedetomidine is used.

A limitation of our study is that it was conducted in healthy volunteers under controlled conditions; results may well differ in patients with some confounding diseases or in a critical care setting. Although the sample size was small, our crossover design easily provided sufficient power to detect differences in BIS values as a function of OAA/S scores. Because we did not measure plasma drug concentrations, we cannot be sure that they remained constant within individuals or that they were similar in each volunteer. Finally, our study was designed to compare 2 well-respected measures of sedation, rather than to determine which test was the “gold standard.” Drugs given via TCI is not the standard clinical application.

In summary, BIS values at an OAA/S score of 2 were about 20 points less with dexmedetomidine than with propofol. OAA/S scores are thus significantly less with dexmedetomidine than with propofol sedation at comparable BIS values. Clinicians using dexmedetomidine for sedation should use BIS and sedation scales in combination for evaluating a patient’s response to sedation.

REFERENCES
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