Assessment of correlation between bispectral index and four common sedation scales used in mechanically ventilated patients in ICU

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Abstract. – Purpose: The aim of this study was to compare the correlation between bispectral index (BIS) monitor and four commonly used subjective clinical scales (Ramsay Sedation Scale (RSS), Richmond Agitation Sedation Scale (RASS), Sedation Agitation Scale, Adaptation to Intensive Care Environment scale) in mechanically ventilated patients in intensive care unit (ICU). In addition, comparison of responsiveness of the clinical scales in respect to BIS changes is another goal of this study.

Materials and Methods: Mechanically ventilated thirty patients who required sedation for any reason were enrolled to study. Patients who needed neuromuscular blockade, patients with known hearing and visual problems, neurological diseases, anoxic encephalopathy, mental retardation and who developed hemodynamic instability (mean arterial pressure below 60 mmHg) and hypoxemia (sPO2 below 90%) during follow-up were excluded. Starting before the initiation of sedation, first BIS scores then clinical sedation scales were evaluated. This procedure is repeated every 2 hours for 24 hours.

Results: All of the four clinical scales were significantly correlated with BIS. BIS and clinical scale values, except Adaptation to Intensive Care Environment scale, showed significant changes compared to baseline after the initiation of sedation. Ramsay and Richmond scales showed the highest correlation with BIS (respectively, r=0.758, r=0.750). Adaptation to Intensive Care Environment revealed the lowest correlation (r=0.565).

Conclusions: All of the scales were significantly correlated with BIS. RSS and RASS showed higher correlation than other scales. As a conclusion: RSS and RASS can be used for monitoring the depth of sedation in mechanically ventilated patients in ICU.

Key Words:

BIS, Sedation scales, ICU (instead of RSS).

Introduction

Patients admitted to the intensive care unit (ICU) may need sedation for variety of reasons including anxiety and pain due to invasive monitoring, endotracheal intubation, mechanical ventilation, medical dressing, awareness of being in the ICU and etc. Sedation can minimize the agitation, anxiety and discomfort associated with the environmental factors and procedures of the ICU.

The primary objective of sedation in the critically ill patients is safety and comfort. Insufficient and excessive sedation have their own handicaps and risks. Insufficient tolerance to the ICU environment might lead to agitation, dysynchrony with the ventilator, increased oxygen demand, hypoxemia, raised intracranial pressure, cardiac failure. Conversely, excessive sedation may decrease consciousness, predisposes the patient to nosocomial pneumonia, contributes to ICU acquired paralysis and prolongs the duration of mechanical ventilation and ICU stay. Hence, monitoring depth of sedation in critically ill patients in ICU is necessary for patients’ safety. Although there is no golden standard for monitoring the level of sedation, some subjective and objective methods are available. Commonly used subjective methods include; Ramsay Sedation Scale (RSS), Sedation Agitation Scale (SAS), the Richmond Agitation Sedation Scale (RASS), scale for Adaptation to the Intensive Care Environment (ATICE). Objective methods include; lower oesophageal sphincter contractility measurement, heart rate variability measurement, evoked potentials, electroencephalography and derived parameters such as Bispectral Index (BIS), Entropy, Patient State Index and Narcotrend.
BIS is a monitor of cortical suppression which may be used to maintain the optimal level of sedation and hypnosis. BIS has proved more reliable than other types of analysis, such as the compressed spectral array (CSA), but may still suffer from some degree of interagent variability. Moreover, patients who have been rendered unconscious following administration of nitrous oxide or fentanyl may exhibit no change in the BIS value during the transition from awake to unconscious. In addition, increasing doses of isoflurane have been shown to cause the expected decrease in the BIS in some patients, no effect in others, and an increase in the BIS in yet others. As in the case for all proposed monitors for depth of anesthesia, BIS does not warn of impending awareness but does indicate that awareness has occurred and may, therefore, reduce the stress suffered from those who are aware, by alerting the anesthesiologist, who can then quickly deepen anesthesia.

Recently, BIS has been proved to be a useful measure of anaesthetic drug effect in pharmacodynamic research and may be useful as a measure of depth of sedation in ICU. BIS offers a continuous single relative number (between 0 and 100) which represents an integrated measure of cerebral activity.

The aim of this study is to measure the level of sedation in mechanically ventilated patients in ICU, using both objective BIS monitor and four commonly used subjective clinical scales (RSS, RASS, SAS, ATICE), and compare the correlation between BIS and clinical scales in a single clinical setting. In addition, comparison of responsiveness of the clinical scales in respect to BIS is another goal of this study.

**Materials and Methods**

The study protocol was approved by Hospital Ethics Committee. Informed consents were taken from the first degree relatives of the patients. Mechanically ventilated thirty patients who required sedation for any reason were enrolled to study. Patients who needed neuromuscular blockade, patients with known hearing and visual problems, neurological diseases, anoxic encephalopathy, mental retardation and who developed hemodynamic instability (mean arterial pressure below 60 mmHg) and hypoxemia (sPO₂ below 90%) during follow-up were excluded.

Decision of initiation and cessation of sedation, choice of sedative agent and dose regimen were made by the ICU physician. The study protocol was conducted by one or two physicians other than the ICU physician. Patients’ ages, weights, genders, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were recorded. Before the initiation of sedation, BIS electrodes were placed on the forehead of the patients, after electrode sites were cleaned with alcohol swabs. Electrodes were connected to ASPECT 2000 BIS monitoring system (Aspect Medical Systems, Norwood, MA, USA). After the Signal Quality Index value displayed on monitor, reached 80-100%, BIS values displayed were registered.

Before the initiation of sedation, first BIS scores then clinical sedation scales; RSS, RASS, SAS, ATICE scores were recorded to avoid BIS score changes influenced by stimulation during execution of the scales. This procedure was repeated every 2 hours for 24 hours. Heart rate, mean arterial pressure, peripheral oxygen saturation values of the patients were also registered at each occasion. If the sedation was interrupted or terminated before 24 hours, scores under sedation were taken into consideration.

**Statistical Analysis**

For statistical analysis MedCalc Version 10.4.6.0 software programme (MedCalc Software, Mariakerke, Belgium) was used. Sample size was estimated as 30 patients to reach a correlation coefficient of 0.6 with type I error (α = 0.05) and type II error (β=0.05). Distribution of data was tested with Kolmogorov-Smirnov test. Repeated measures ANOVA test and Friedman test was utilized for comparison of data according to results of distribution test. For analysis of correlation of clinical scales and BIS monitor, Spearman’s rank test and for the dual comparison of correlation coefficients, z test were utilized. Values of \( p < 0.05 \) were considered significant.

**Results**

The patient data and APACHE II scores are listed in Table I. Mean arterial pressures, heart rates and peripheral oxygen saturations of the patients did not show statistically significant changes compared to baseline values throughout the study (\( p > 0.05 \)).
Sedation is an integral part of the management of critically ill patients admitted to the ICU, especially for those being treated with mechanical ventilation. Sedation monitoring in ICU is necessary to avoid the complications related to both under and over sedation which have obvious effect on morbidity and mortality in ICU. Many objective and subjective methods have been proposed for sedation monitoring in ICU.

BIS is an objective method of monitoring sedation which combines the frequency domain analysis of the electroencephalogram (EEG) with the qualification of the degree of phase coupling between the waves included in the EEG. Data obtained from a great number of EEG tracings submitted to bispectral analysis were correlated with different clinical levels of the employed drugs, allowing the elaboration of a numerical scale. BIS monitor offers a distinct advantage of objective, non-invasive, practical and bedside-time assessment of the sedated patient without the application of external stimuli. BIS values also correlates well with the reduced metabolic rate of the brain. BIS might be an accurate method for assessing and controlling deep sedation in ICU patients than clinical sedation scores. BIS values also show significant correlation with duration of sedation and dosages of sedative agents.

Subjective methods are based on the clinical evaluation of the level of sedation. Direct clinical observation allows a rough distinction between adequate, excessive and inadequate sedation. Most of the clinical scales use only verbal or physical stimuli for categorical evaluation of sedation or agitation which is not fully definitive but they are easy to perform, cheap and correlates well the objective methods. To obtain a more quantitative description of the level of sedation with better reliability, more than 30 evaluation scales have been proposed. The most studied are RSS, RASS, SAS, Comfort Scale, Glasgow Coma Scale and ATICE for ICU patients. Starting from this point, we investigated the correlation of an objective method of monitoring sedation, BIS, with the subjective methods which are RSS, RASS, SAS and ATICE in our study.

One of the problems which cause mismatch between the results of BIS monitor and clinical scoring systems of sedation is the timing of BIS measurement. Using clinical scales for assessment of depth of sedation, verbal or painful stimuli are used. These stimuli causes an increase in

<table>
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<th>Table I. Characteristics of the patients.</th>
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<tr>
<td>Gender [F (%)/M (%)]</td>
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<tr>
<td>Age (Mean ± SD) (years)</td>
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<tr>
<td>Weight (Mean ± SD) (kg)</td>
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<tr>
<td>APACHE II (Median (min-max))</td>
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Figure 2. A-E. Values of BIS and clinical scales before and after initiation of sedation (values are expressed as median min-max). *p < 0.05 vs.
BIS value. So timing of the BIS measurement changes the BIS value and hence the correlation between BIS and clinical sedation scores. We first registered the BIS value and then we performed the clinical evaluation of sedation scale.

RSS is described in 1974. It has been and still is, the most commonly used to monitor the level of sedation in ICU. RSS categorizes the response of the patient to verbal and physical stimuli. It is easily performed at bedside. Studies demonstrated strong correlation of RSS with BIS and evoked potentials in different subgroup of patients in ICU. RSS is used as a reference to evaluate and validate the other subjective clinical scales. In our study, similar to the values of reported literature, the highest value of correlation coefficient between BIS and the clinical scales, was of RSS ($r=-0.758$). RSS values significantly decreased after initiation of sedation, similar to BIS values, means RSS well responded the changing sedation level.

RASS is developed with the collaboration of ICU physicians, nurses and pharmacologists. It is consisted of ten levels which four levels describe anxiety and agitation, and five levels describe sedation. Describing 10 levels of sedation and agitation is advantageous over other clinical scales.

Table II. Comparison of correlation coefficients of clinical scales.

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<tr>
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<th>$z$ statistics</th>
<th>$p$ value</th>
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<tr>
<td>BIS-ATICE vs BIS-RASS</td>
<td>4.6295</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>BIS-ATICE vs BIS-RSS</td>
<td>4.8875</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>BIS-RASS vs BIS-SAS</td>
<td>2.0255</td>
<td>$p = 0.0428$</td>
</tr>
<tr>
<td>BIS-RASS vs BIS-SAS</td>
<td>0.2579</td>
<td>$p = 0.7965$</td>
</tr>
<tr>
<td>BIS-RSS vs BIS-SAS</td>
<td>2.6040</td>
<td>$p = 0.0092$</td>
</tr>
<tr>
<td>BIS-RSS vs BIS-SAS</td>
<td>2.8619</td>
<td>$p = 0.0042$</td>
</tr>
</tbody>
</table>

Figure 2. A-D. Scatter plots and regression lines for BIS and sedation scales ($r =$ correlation coefficients).
scales. Ely et al\textsuperscript{21} demonstrated a strong correlation between BIS and RASS in two different studies ($r=0.70$ and $r=0.63$) and they also pointed out validity and inter-rater reliability of RASS\textsuperscript{21,22}. Turkm en et al\textsuperscript{23} found a significant high correlation between BIS and RASS with 11 mechanically ventilated ICU patients ($r=0.9$). In our study BIS and RASS correlation was statistically significant similar to other investigations in literature, the correlation coefficient was 0.750 with significant responsiveness.

SAS was composed by Riker et al\textsuperscript{24} to evaluate the sedative effect of haloperidol in 1994. In 1999 they demonstrated the validity and reliability of SAS comparing with RSS. The basic difference between SAS and RSS is that the agitation is defined in single step in RSS but in three steps in SAS\textsuperscript{19}. The correlation between BIS and SAS had been evaluated in a number reports with different study designs. Results of these studies revealed statistically significant but fairly low correlation coefficients ranging from 0.14 to 0.48. In one of these works, the correlation did not exist in some subgroups\textsuperscript{25-27}. With our study design the correlation between BIS and SAS was statistically significant and correlation coefficient was fairly higher ($r=0.656$). Our results indicated better correlation between BIS and SAS when compared with the results in literature.

De Jonghe et al\textsuperscript{28} developed and validated the ATICE to evaluate the adaptation of mechanically ventilated patients to the intensive care environment by measuring the consciousness and the tolerance of the patient. They demonstrated ATICE had good validity, reliability and responsiveness in mechanically ventilated critically ill patients. Low scores reflect poor adaptation to ICU environment. It is consisted of five categories; awareness, comprehension, calmness, ventilator synchrony and face relaxation. In our research the correlation between ATICE and BIS was statistically significant ($r=0.565$) but the correlation was lower when compared with the other clinical scales. Since there are a few studies about ATICE scale we couldn’t compare our findings with the results in literature. ATICE values did not change statistically in respect to baseline ATICE values after initiation of sedation. ATICE scale showed lower responsiveness than other scales tested in the study. This result is thought to be related with the different structure of the scale composed of domains like consciousness and tolerance.

In our investigation we aimed to detect and compare the correlation between BIS and four commonly used subjective clinical scales in a single study. All of the scales tested were significantly correlated with BIS. Most commonly used scales, RSS and RASS showed higher correlation than other scales. ATICE scale revealed the lowest correlation with BIS. The differences between the correlation coefficients of the scales were statistically significant. All scales responded the BIS changes after sedation except ATICE.

Conclusions

RSS and RASS can be used for monitoring the depth of sedation in mechanically ventilated patients in ICU.

References

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