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Is the bispectral index appropriate for monitoring the sedation level of mechanically ventilated surgical ICU patients?

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Abstract *Objective:* To determine the value of the bispectral index (BIS) in assessing the depth of sedation in sedated and mechanically ventilated ICU patients, compared with clinical sedation scores. *Design and setting:* Prospective convenience sample in a 12-bed anesthesiological-surgical ICU of a university hospital. *Patients:* 19 consecutive patients without any central neurological diseases requiring mechanical ventilation for more than 24 h. *Measurements:* BIS version 3.12 and clinical depth of sedation assessed by the modified Observers's Assessment of Alertness/Sedation Scale, modified Glasgow Coma Scale, modified Ramsay Scale, Cook Scale, and Sedation-Agitation Scale were measured twice daily while patients were intubated and once daily after extubation until discharged from ICU. *Results:* there was a moderate correlation between BIS and each sedation score in 11 patients (58%, "BIS patients") and no correlation in 8 patients (42%, "non-BIS patients"). We found no parameters distinguishing between these two groups. On average eight measurements were necessary to establish a statistical correlation. In the BIS patients the slopes of the linear regression curves showed significant differences for all BIS score combinations with increasing scattering at deeper sedation levels. *Conclusions:* BIS is correlated only in some ICU patients with the clinical assessment of their sedation level as based on various scores. At deeper sedation levels the interindividual differences increase. There were no criteria found to distinguish patients with and without correlation. This suggests that the BIS is not suitable for monitoring the sedation in a heterogeneous group of surgical ICU patients.

Keywords Bispectral index · Intensive care · Sedation scale · Electroencephalogram

Introduction

Monitoring the depth of sedation in mechanically ventilated ICU patients is not yet satisfactory [1]. Subjective clinical scores are normally used which have not been sufficiently investigated regarding their reliability, validity and sensitivity to changes in depth of sedation (responsiveness) [1, 2]. The bispectral index (BIS) derived from electroencephalography (EEG) could be an alternative objective parameter [2, 3, 4], making this index as a promising approach for assessing the depth of hypnosis during anesthesia [5, 6, 7, 8, 9].

BIS appears more reliable than other processed EEG parameters, such as the spectral edge frequency and the median frequency, in determining the degree of sedation [5, 10]. BIS is a promising parameter for monitoring sedation on ICU despite evidence that the administration of opioids reduces the validity of BIS [11, 12] as the blockade of nociceptive afferences apparently is not detected [13]. More studies to verify its reliability and validity are required [2, 3].

Only few authors have studied the validity of the BIS in ICU patients. In 11 patients during rapid terminal weaning from mechanical ventilation Campbell et al. [14] found a moderate correlation (r=0.5279–0.5807, p<0.001) between BIS and two sedation scales (Bizek Agitation Scale, Comfort Scale). Simmons et al. [15, 16] also found a moderate correlation between BIS and the Sedation- Agitation Scale for 63 patients monitored during 64 episodes of ventilatory support (r^2=0.21, p<0.001). Further analysis of this study, however, reveals that such a correlation applies only for trauma patients and patients undergoing cardiac surgery (p<0.018), not for patients undergoing general surgery or ICU patients of internal medicine (p>0.19). The results reported by Simmons et al. [15] even suggest that BIS may not be suitable for monitoring sedation of ICU patients in general [17, 18, 19].

This study examined the value BIS in determining the depth of sedation in a heterogeneous series of sedated surgical patients being ventilated in a ICU.

Materials and Methods

We intended to study prospectively 22 patients requiring mechanical ventilation for at least 24 h. This size of group is considered ideal for detecting a large effect of coherence Δ with a test power of ε=0.8 and a defined level of significance p<0.05; the null hypothesis may then be rejected [20]. We examined only 19 patients, because with this size of group we had to accept the zero hypothesis. Patients' demographic data, duration of ICU stay, and principal diagnoses are presented in Table 1. The study was conducted in accordance with the 1964 Declaration of Helsinki and received the approval of the local ethics committee. If possible, the patients gave their written informed consent before being operated. In other cases of unanticipated mechanical ventilation, such as in polytraumatized patients, consent was obtained from the relatives. Exclusion criteria were age under 18 or over 65 years [21], diseases of the central nervous system including hypacusis, severe head injury, alcoholism, and hepatic or renal failure [22]. Neuromuscular relaxation was excluded with an acceleromyographic monitor (TOF-Watch, Organon-Teknika, The Netherlands).

BIS was measured with an A 1000-monitor version 3.12 (Aspect Medical Systems, Natticks, Mass., USA) twice daily until extubation, and thereafter once daily until patients were discharged from ICU.

Low- and high-pass filters were set at 0.25 and 30 Hz; the smoothing rate was 10 s. Electrocardiographic (ECG) gel was applied to the Ag/AgCl ECG electrodes (no. 2223, 3M Health Care, Germany) [23] to reduce electrode impedance under 5 kΩ and then placed frontocentrally (FP1-FPZ, FP2-FPZ) [24]. To avoid arousal reactions an interval of 15 min without any manipulation of the patient was passed before beginning the measurement. Then the BIS was averaged over 50 s. Phases of bad EEG quality were ignored. Thereafter the clinical depth of sedation was assessed by the modified Observer's Assessment of Alertness/Sedation Scale [9], the modified Ramsay Sedation Scale [25], the Sedation-Agitation Scale [17], the modified Glasgow Coma Scale [26], and the Cook Sedation Scale [27]. As a noxious stimulus required in some scales for patients with very deep sedation, we used a tetanic stimulus with 50 Hz/50 mA for 10 s applied by a peripheral nerve stimulator (NS 252, Fisher & Paykel, Auckland, New Zealand) via ECG electrodes mounted over the tibial bone [28]. If inaccessible, the electrodes were attached to the lateral radius.

All drugs administered during the previous 24 h and the present hemodynamic and the laboratory parameters were recorded by the CareVue Documentation System (Hewlett Packard, Böblingen, Germany). The sedation regimen was chosen by the ICU team adapted to clinical necessity and was composed of fentanyl and midazolam. In addition ketamine, clonidine, piritramide, or flunitrazepam was given.

The statistical analysis was performed with SPSS 10.0. Because of the ordinal scale levels of BIS and the sedation scales

Table 1 Patients demographic and statistical data of the correlation between BIS and sedation scores (*DV* duration of mechanical ventilation, *DIS* duration of ICU stay, *Ms* number of measurements)

Patient no.	Sex	Diagnosis	DV/DIS (days)	Age (years)	Height (cm)	Weight (kg)	Ms	p^a	τ^a
1	F	Oropharyngeal carcinoma	10/11	42	168	65	13	<0.005	0.66–0.86
2	M	Multiple injuries	6/7	20	185	92	7	>0.06	–
3	F	Multiple injuries	26/30	31	170	70	29	<0.0001	0.60–0.64
4	M	Abdominal lavage	29/36	63	170	110	49	<0.0001	0.59–0.76
5	M	Multiple injuries	5/5	44	178	85	6	<0.05	0.75–0.79
6	M	Multiple injuries	11/13	27	180	76	17	>0.3	–
7	F	Multiple injuries	5/6	21	167	53	6	>0.05	–
8	M	Oropharyngeal carcinoma	8/10	47	175	95	14	<0.005	0.63–0.66
9	F	Abdominal lavage	7/9	50	165	120	7	>0.05	–
10	M	Multiple injuries	7/11	24	180	75	12	<0.001	0.76–0.79
11	M	Esophageal perforation	8/9	59	175	95	10	<0.05	0.55–0.72
12	F	Oropharyngeal carcinoma	3/4	58	165	90	5	>0.07	–
13	M	Oropharyngeal carcinoma	4/5	50	170	75	5	<0.05	0.95–1.0
14	F	Flap reconstruction	8/11	58	165	90	10	<0.005	0.73–0.79
15	M	Multiple injuries	27/30	41	170	80	21	<0.005	–
16	M	Multiple injuries	3/4	19	178	84	3	>0.1	0.87–1.0
17	M	Multiple injuries	10/15	53	165	70	5	>0.05	–
18	F	Multiple injuries	30/33	51	163	65	5	>0.1	–
19	M	Esophageal carcinoma	39/40	56	170	110	23	<0.0001	0.68–0.73
Mean	–		13/15	43	172	84	247	–	–

[a] Refers to range over all five scores

Table 2 Demographic data and differences between patients with (*BIS*) and without (*Non-BIS*) correlation between bispectral index and sedation scores

	BIS (*n*=11)	Non-BIS (*n*=8)	*p*
Age (years)	45	40	NS
Sex: M/F (%)	27/73	38/63	NS
Body mass index	28.0	29.2	NS
Duration of ICU stay (days)	16.0	14.6	0.0003
Duration of mechanical ventilation (days)	13.4	12.4	0.033
Temperature (°C)	38.1	38.0	0.016
Quick (%)	79	86	0.005
Glutamic oxaloacetic transaminase (U/l)	18	30	0.0009
Glutamic pyruvic transaminase (U/l)	29	31	0.031
Bilirubin (µmol/l)	17.2	15.1	0.035
Hemoglobin (mmol/l)	5.7	5.4	0.0002
Creatinine (µmol/l)	69.6	85.1	0.015
Blood urea nitrogen (mmol/l)	3.2	3.0	0.023
Glutamic acid (mmol/l)	8.45	7.61	0.0025
Piritramide[a] (mg)	0.11	1.83	0.018

[a] Administered in the last hour before measurement

Kendall's τ stastistic was used to assess correlations. The slopes of the linear regression curves were compared by the Draper and Smith method. The χ^2, Student's *t*, and the *U* tests were used to analyze the differences between groups.

Results

The intravenous administration rate of sedation drugs per hour was 0–21 µg/kg fentanyl and 0–430 µg/kg midazolam; two patients with a high-dose of fentanyl and midazolam also received 0.4–5.7 mg/kg ketamine. During weaning and agitation 0.33–6.0 µg/kg clonidine was administered intravenously per hour and in cases of pain 35–105 µg/kg piritramide.

For the overall series BIS was correlated with all five scores ($\tau>0.5906$, $p<0.0001$). Individual analysis, however, verified this moderate correlation for only 11 of the 19 patients (58%; $0.55<\tau<1.0$, $p<0.005$; Fig. 1). In these "BIS patients" the BIS was correlated with all five scores while in the eight "non-BIS patients" the BIS was not correlated significantly with any score (Table 1, Fig. 2). Table 2 compares the demographic characteristics of BIS and non-BIS patients. None of the parameters at first measurement in patients indicated anything about their respective "BIS qualification."

In two patients ketamine was used in addition to fentanyl and midazolam. Patient no. 3 received ketamine at 6 of 29 measuring points. Mathematically all 29 measuring points in this patient indicated a significant correlation (Table 1). Figure 1, however, shows that during deep sedation as judged by clinical assessment, there were BIS values up to 94 when ketamine was administered. In another case, that of patient no. 9, there was no significant correlation either with or without ketamine (Table 1), even though there was a tendency to BIS values when the patient was deeply sedated (Fig. 2). A significant relationship for the correlation between BIS and score is seen at the earliest after 4–15

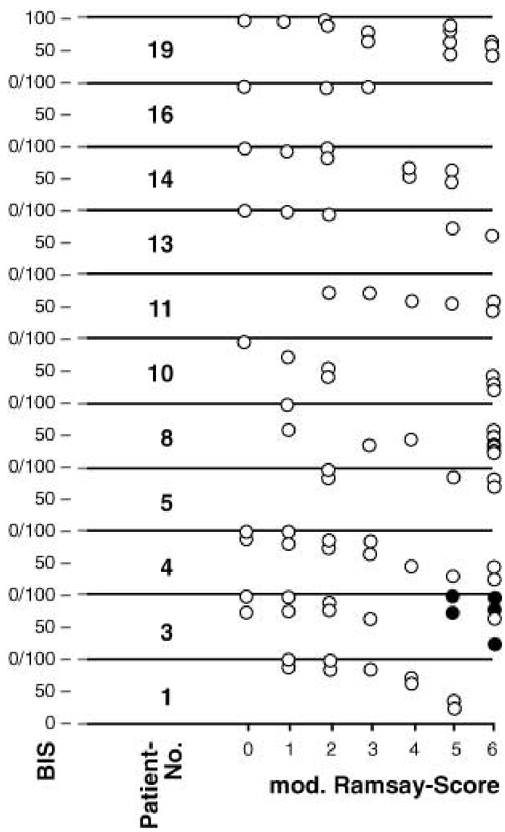

Fig. 1 Measurements of bispectral index (BIS) and modified Ramsay Sedation Scale for patients with correlation between BIS and sedation scores. *Filled circles* Ketamine. ($p<0.05$, τ)

measurements (mean 8.4) with no differences between the scores.

The analysis of variance for assessing the slope of the regression lines in the BIS patients showed differences in all BIS score combinations ($p<0.01$). Figure 3 shows as an example the regression line for BIS and modified Ob-

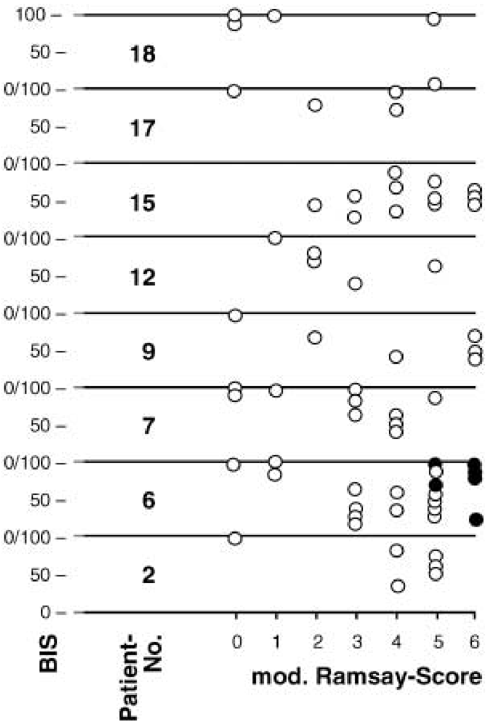

Fig. 2 Measurements of bispectral index and modified Ramsay Sedation Scale for patients without correlation between BIS and sedation scores. *Filled circles* Ketamine. ($p<0.05$, τ)

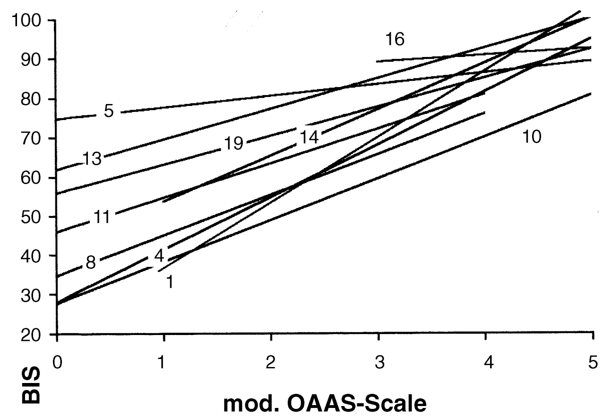

Fig. 3 Linear regression curves (numbered as in Fig. 1) for patients with correlation between BIS and sedation scores. Following the Draper and Smith method, the slopes of the regression curves are significantly different ($p<0.01$)

server's Assessment of Alertness/Sedation Scale. Variance on all scores increased at deeper levels of sedation.

Discussion

Development and use of objective methods to assess the depth of sedation in patients being mechanically ventilated on the ICU gives hope for a decrease in morbidity and mortality in reducing stress of the organs [17]. Furthermore, the avoiding of oversedation, a shortening of ICU stay, and a decrease in cost can be expected [2]. Clinical scores normally used for assessing the depth of sedation are inadequate concerning validity, reliability, and responsiveness [1, 29]. They also fail in cases of very deep sedation, neuromuscular relaxation, hypacusis, and locked-in syndrome.

An objective approach to assess the depth of sedation of ICU patients is the computerized interpretation of the cortex EEG as an expression of cerebral activity [22]. Only few studies have attempted to validate such parameters in the ICU. Freye et al. [30] found a relationship between preselected dose of midazolam/alfentanil and the SEF 95 in ten patients. Albrecht et al. [31] and Frenkel et al. [32] used the median frequency for closed-loop sedation in ICU patients receiving propofol with or without alfentanil until they tolerated mechanical ventilation. Polytraumatized patients, however, required greater suppression of EEG activity (MF 1–2 Hz) than patients without trauma (MF 2–3 Hz). Individual differences for BIS in the same clinical depth of sedation have also been observed [15]. A disadvantage of frequency domain methods such as MF and SEF is the EEG activation caused by hypnotics in lighter levels of sedation [21] with an initial increase in these parameters. Therefore there is no monotonic relationship. The algorithm generating BIS avoids this increase by composing BIS on the basis of weighted subparameters [4].

This study investigated whether the correlation between BIS and clinical scores can be used to assess the degree of sedation in a heterogeneous group of ICU patients. Various clinical scores have been used to determine the depth of sedation in the ICU. None of these scores, however, has been examined thoroughly with regard to reliability, validity, and sensitivity to detect changes in the depth of sedation [1]. The levels of the Ramsay Scale as the so-called "gold standard" [2] do not seem to be mutually exclusive nor clearly defined or fully inclusive, and they fail to define clear endpoints of sedation [29]. Therefore, if a new monitoring system such as BIS is to be validated, one must rely on somewhat deficient scoring systems as a reference, as more valid systems are lacking. For this we used five different scoring systems to avoid an insufficient correlation between BIS and a single score because of its deficiencies.

As in earlier studies [14, 15], data from all 19 patients together showed a correlation between BIS and all tested clinical scores. The individual analyses, however, found BIS to be unsuitable in 42% of the patients. This observation is similar to results reported by Simmons et al. [15] who found a correlation between BIS and Sedation- Agitation Scale only in trauma patients ($r^2=0.52$, $p=0.018$, $n=10$), at best for patients undergoing cardiac surgery ($r^2=0.25$, $p=0.008$, $n=27$). No correlation was seen in patients after general surgery (r^2=0.26, p=0.26, p=0.2, n=8) or in patients in an ICU for internal medicine (r^2=0.10, p=0.19, n=19). It is unclear whether Campbell et al. [14] found a correlation for every single patient. Regarding the comparability of the statistical results in the above mentioned studies it must be noted that Spearman's rank correlation, as used in these studies, is an appropriate test for investigating cardinally scaled data. BIS and sedation scores are ordinal scales with intervals of dissimilar attributes. In this case Kendall's τ must be used [20].

No reasons could be found for the lack of suitability of almost one-half of the patients. Ketamine is known to activate the EEG and therefore produces higher BIS values than the clinical depth of sedation [33, 34]. On the other hand, the reliable use of the BIS with ketamine and propofol anesthesia has been reported [35]. In our study two patients received ketamine in addition to fentanyl and midazolam. In both cases there was a tendency towards higher BIS values in clinically deeply sedated states. The small number of cases does not allow reliable evaluation. Graphic analysis of the non-BIS patients shows a great dispersion of BIS values, with no uniform aberration towards one direction (Fig. 2).

O'Connor et al. [36] made similar observations in 29 patients with neurological diseases. Nine patients had BIS values that were too high in relation to the Observer's Assessment of Alertness/Sedation Scale and Ramsay Scale. Three of these patients had an increased electromyographic (EMG) activity; even two patients with falsely low values were seen. EMG artifacts were discussed as a possible reason for the variance in the BIS, as these are known to influence the BIS toward higher values [37]. In our study we did not perform EMG; however, this is possible with newer BIS versions. We saw one patient (no. 11) who was shivering at a temperature of 38.7°C and receiving fentanyl and flunitrazepam. With a BIS value of 98, he was deeply sedated and reacted only to noxious stimulus and endotracheal suction. For statistics this measurement was seen as an exception even though this measurement does not impair the BIS correlation with all five scores.

BIS and non-BIS patients could not be distinguished on the basis of limited and clinical practically numbers of BIS measurements. On the average eight measurements (in approx. 4 days) were necessary to establish a statistical correlation.

Assuming a first-order relationship between BIS and clinical sedation level, the slope of the regression line shows clear differences between the BIS patients as an expression for increasing interindividual differences in deeper levels of sedation (Fig. 3). This is in accord with observations by De Deyne et al. [17] in 18 ICU patients with BIS values of 15–65 (mean 62) in the same clinical level of sedation (Ramsay 6) whereas the stimulus was not reported. The authors interpreted this dispersion in values as an oversedation having BIS values of less than 60. Another possible reason is the great interindividual BIS variability that we observed. In BIS patients with an averaged BIS of 57 we saw a modified Ramsay score of 4–5, while patients with a BIS of 44 had a score of 6. These differences may be due to the use of morphine instead of fentanyl or to the use of a less noxious stimulus to exclude a Ramsay 5 sedation. This suggests that if the BIS monitor can be used to control sedation, it must be calibrated for every patient individually, which cannot be justified in these patients. Barr et al. [12] and Driessen et al. [38] reported a wide variance in patients undergoing cardiac surgery receiving fentanyl/midazolam anesthesia, and they therefore rejected the use of BIS with this kind of anesthesia.

In summary, this study found that the BIS was correlated with the clinical depth of sedation in only some of the 19 sedated surgical patients in the ICU. No explanation for the unsuitability of BIS in 42% of the patients was found, as it also remained unclear how to discriminate between BIS and non-BIS patients. Moreover, BIS patients showed a wide interindividual variance in BIS values with increasing depth of sedation.

The results of our study suggest that BIS in the tested version (3.12) is not suitable for monitoring the sedation in surgical ICU patients. It therefore remains a valuable goal to develop a parameter that allows accurate grading of sedation levels in ICU patients. More studies are required to investigate whether newer BIS versions or other electrophysiological monitors such as Narcotrend (MT MonitorTechnik, Bad Bramstedt, Germany) or A-line AEP Monitor (Alaris Medical Systems, Hampshire, UK) can do so.

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