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Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients

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Abstract Monitoring the depth of sedation in patients under intensive care is difficult. Clinical assessment by the different scoring systems produces insufficient information, especially once deeply sedated patients become unresponsive to any external stimulation. Recently, the bispectral index (BIS), the result of computerized bispectral electroencephalographic monitoring, was found to be the best predictor of depth of anaesthesia during surgical intervention. This report concerns BIS monitoring in 18 randomly selected, deeply sedated, surgical patients in the intensive care unit, who were unresponsive to standard clinical stimulation (Ramsay sedation score). A wide range of BIS was observed, with 15 of the patients having a BIS below 60, indicating a state of deep sedation (or possibly oversedation). Therefore, further studies using BIS monitoring in patients under intensive care are needed to determine if this method can guide sedation and prevent oversedation in this context and, most importantly, to analyse its final cost – benefit ratio.

Key words Bispectral index · Electroencephalogram · Intensive care sedation

Introduction

Monitoring depth of sedation in critically ill patients in an intensive care unit (ICU) is difficult. Clinical assessment by the various scoring systems available produces insufficient information, especially once deeply sedated patients become unresponsive to any external stimulation [1, 2]. This deep sedation is sometimes needed as part of the treatment for intracranial hypertension or to enable pressure-controlled ventilation in the presence of the adult respiratory distress syndrome. Nevertheless, excessive levels of sedation might have important implications for morbidity and mortality, and for the costs of intensive care.

Cerebral function monitoring by processed electroencephalography (EEG) is potentially valuable in the ICU because it can be used to test the end result of the chosen sedation at the neuronal level. Processed EEG monitoring will continue to provide information on cerebral function when clinical assessment is no longer possible, as is the case in patients with a maximal Ramsay sedation score, who are unresponsive to any external stimulation. The use of processed EEG variables to assess depth of sedation remains controversial. Veselis et al. [3] correlated several power-spectral EEG variables with the clinical level of sedation and concluded that the main effect of midazolam sedation was a shift of the dominant power from high to low frequencies as the sedation level increased, and the spectral-edge frequency 95% (SEF 95% = the frequency below which 95% of the total power is contained) was found to be the most sensitive measure of depth of sedation. Shearer et al. [4] reported on the use of the Cerebrotrac 2500, providing a real-time spectral analysis, for continuous monitoring of cerebral function in ICU patients receiving midazolam, morphine and propofol. The processed EEG patterns could not be correlated precisely with a standard clinical scoring system but were useful in deter-

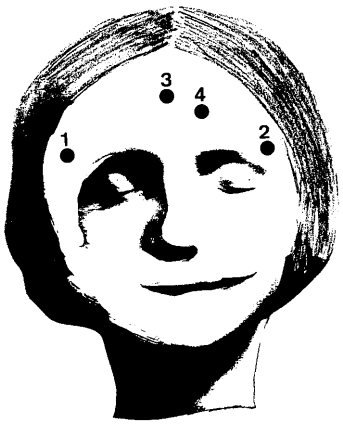

Fig. 1 International 10/20 system with the montage used. *1* channel 1, *2* channel 2, *3* reference, *4* ground

mining the adequacy of sedation, particularly when a muscle relaxant was used. They also reported that excessive sedation was characterized by continuous delta activity.

Recently, the bispectral index (BIS), a new processed EEG measurement, 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 [5]. BIS offers a continuous, single relative number (between 0 and 100) which represents an integrated measure of cerebral electrical activity. It is designed to correlate with hypnotic endpoints and capable of accounting for the majority of EEG patterns produced by anaesthetics and sedatives [6, 7]. Compared with classical power-spectral analyses, which use the frequency and amplitude of the raw EEG signal to compute a processed univariate parameter [6], the BIS proprietary algorithm uses not only a complex Fourier transformation but also includes information about the influence of interrelations between different frequency components (phase coupling), beta-activation and isoelectricity. Liu et al. [8] proved the usefulness of the BIS in the operating room to monitor depth of midazolam-induced sedation during surgery. Preliminary reports [9] on its use in ICU patients reveal a good correlation between the BIS and the Ramsay sedation score, which is still the 'gold standard' for assessing clinically the depth of sedation in ICU patients.

When measuring EEG in an ICU, it is important to assess the quality of the EEG signal. There are many problems with signal bias due to electrical interference from other equipment used in the ICU. So, when evaluating a new monitoring device, it is important to assess signal quality and accuracy.

The aim of this study was to make a first limited observational feasibility report on the use of continuous BIS analyses in a small number of ICU patients who were deeply sedated and unresponsive to any external stimulation. We were especially interested to know if BIS monitoring might reveal a wide variation in depth of sedation in those heavily sedated patients receiving sedation for more than 72 h, and in whom deep ICU sedation was advocated for systemic pathology. We also aimed to evaluate the possibility of obtaining a high-quality EEG signal in the ICU.

Patients and methods

Eighteen randomly selected, surgical ICU patients, who had received a standardized sedation regimen for more than 72 h, were monitored with BIS. Only patients who were deeply sedated with no response to any external stimulation, evaluated by having a Ramsay sedation score of 6 [9], were included.

All patients were sedated with morphine and midazolam to achieve and maintain a Ramsay sedation score of 6, with a starting dose of 0.15 mg/kg per h of morphine and 0.2 mg/kg per h midazolam. No bolus injections of morphine or midazolam were given. If sedation was insufficient, as shown by a decrease in the Ramsay sedation score, continuous infusion rates were increased (steps of 0.05 mg/kg per h for both drugs). If haemodynamic instability (mean arterial pressure < 70 mmHg) occurred, the infusion was decreased (steps of 0.05 mg/kg per h for both drugs). In none of these patients any other sedative drug was given. An Acute Physiology and Chronic Health Evaluation (APACHE) II score was recorded in all patients. Standard biochemical analyses to investigate renal (creatinine clearance < 30 ml/min) and liver failure (prothrombin time less than 30 % of original value) were performed daily.

BIS was measured with an Aspect A-1000 EEG analyser (Aspect, Natick, USA) with ZipPrep electrodes (Aspect). A bifrontal referential montage (F7-Fz; F8-Fz, using the International 10/20 system for EEG montage) was applied, as shown in Fig. 1. Electrode impedance was maintained below 5000 Ω to ensure adequate signal quality. Artefacts due to poor signal quality were automatically detected, recorded on hard disk and excluded from further analysis. A signal quality index (SQI), automatically calculated by the Aspect A-1000 EEG analyser, was used to evaluate the quality of the measured EEG signal. An adequate EEG signal must obtain an SQI of between 80 and 100 %. The BIS (calculated for each 4 -s epoch) and its trend were displayed on screen. All patients were monitored for a period of 2 h. BIS was recorded each minute and a 2-h average was calculated for every patient.

For statistical analyses the *t*-test was used. Significance was set at 5 %. Correlation between BIS, duration of sedation and dosages of both sedatives were analysed by Spearman's rank correlation.

Results

All results are given as median (range), except as indicated. In all patients, EEG monitoring was performed easily without major technical interference in this ICU environment. The SQI during measurement was always above 80 %.

As shown in Table 1, all patients were sedated for between 4 and 6 days. The sedation regimen during the BIS recording period is shown in Table 1. The APACHE II score was 19 (12–28) (see Table 1). Individual results for liver and renal failure are shown in Table 1. Renal failure occurred in 8/18 patients, liver failure in 6/18. Among all the patients suffering from renal

Table 1 Patients' individual results. (*BIS* bispectral index, *DS* duration of sedation, *RF* renal failure, *LF* liver failure, *MOF* multiple organ failure, *ARDS* adult respiratory distress syndrome)

Patient	BIS	DS (days)	Apache II	RF	LF	Morphine (mg/kg per h)	Midazolam (mg/kg per h)	Patholoy
1	30	4	12	No	No	0.15	0.2	Severe head injury
2	25	5	14	No	No	0.1	0.15	Intracranial bleeding
3	25	5	12	Yes	No	0.1	0.15	MOF
4	55	4	16	No	No	0.15	0.15	Severe head injury
5	30	5	16	No	No	0.15	0.15	ARDS
6	20	5	12	No	No	0.15	0.2	Severe head injury
7	15	4	16	Yes	No	0.1	0.15	MOF
8	15	4	23	Yes	Yes	0.15	0.2	Multiple injuries
9	30	6	20	No	No	0.15	0.15	Multiple injuries
10	50	4	18	Yes	Yes	0.1	0.15	MOF
11	40	5	20	Yes	Yes	0.1	0.2	MOF
12	65	6	27	Yes	Yes	0.15	0.15	MOF
13	45	5	28	No	No	0.15	0.2	Multiple injuries
14	20	6	15	Yes	Yes	0.1	0.15	MOF
15	35	4	27	No	No	0.1	0.15	Intracranial bleeding
16	60	4	22	No	No	0.15	0.2	Severe head injury
17	45	4	20	No	Yes	0.1	0.15	Liver transplant
18	20	5	28	Yes	No	0.1	0.15	MOF

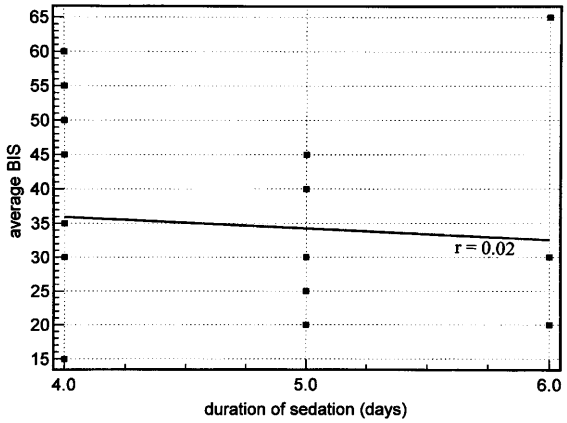

Fig. 2 Correlation between average BIS and duration of sedation

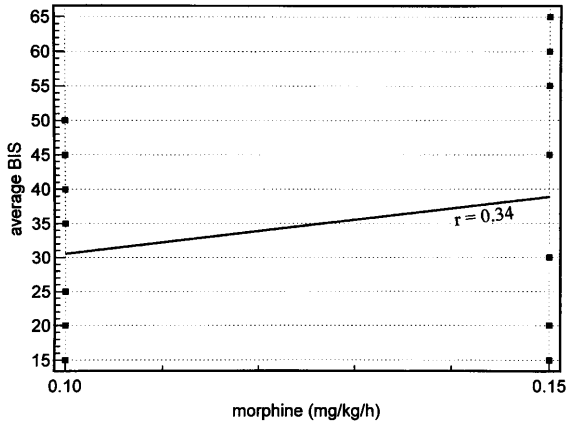

Fig. 3 Correlation of average BIS and dosage of morphine

failure, only patients 7 and 8 received continuous renal replacement therapy at the time of the measurements. Individual averaged results of BIS measurements are given in Table 1. The average BIS in the whole population was 34 (15–65). Of the 18 patients, 15 had an average BIS below 60; for 7/18 patients, the average BIS was below 30.

The results of correlations between the patients' average BIS and duration of sedation, dosages of morphine, dosages of midazolam are shown in Figs. 2, 3 and 4, respectively. Patients with renal failure had an average BIS of 31 (15–65) and these without renal failure 37 (20–60), with no statistical significance between groups. Patients with liver failure had an average BIS of 39 (15–65) and those without liver failure 32 (15–60), also with no significance between the groups.

Discussion

Sedation is an integral part of the management of critically ill patients admitted to the ICU. Its primary objectives are to enhance patient comfort, reduce anxiety and disorientation, facilitate sleep, and minimize resistance to mechanical ventilation [1]. Monitoring depth of sedation in ICU patients is challenging. Clinical scoring systems have been developed as an objective means of assessing depth of sedation. The scoring system currently used, the Ramsay sedation score, provides a means of measuring the patients' level of responsiveness and sleepiness in the ICU. It is an objective measurement of the effects of pharmacological sedation. Unfortunately, the extremes of possible consciousness dysfunction

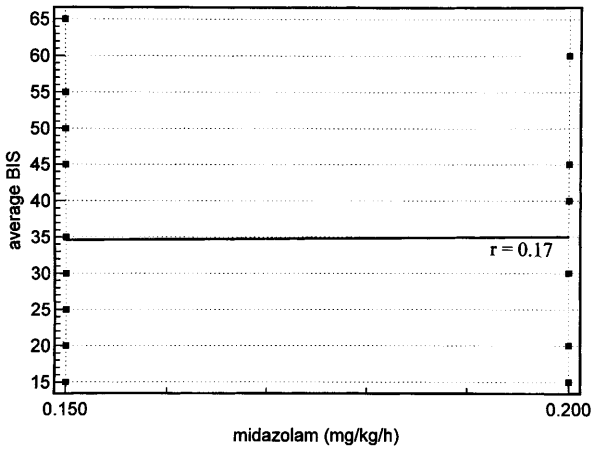

Fig. 4 Correlation between average BIS and dosage of midazolam

are ineffectively measured, as agitation and oversedation are not easily evaluated with this scale [10]. The Ramsay sedation score is useless when the visual effects of sedative adequacy disappear, as, for example, with therapeutic musculoskeletal paralysis or when a deep level of sedation is necessary.

Oversedation from sedatives and analgesics is a real problem in ICU patients. Despite the necessity of (sometimes deep) sedation in ICU patients to avoid their fighting the ventilator or to prevent dangerous increases in intracranial pressure, oversedation has important implications for morbidity and mortality, and inherent implications for ICU costs. Changes in the pharmacokinetics and pharmacodynamics of sedative and analgesic drugs in critically ill patients may be a main cause of oversedation [11, 12]. Shelly et al. [13] reported the impaired ability of critically ill patients with septic shock to metabolise midazolam, possibly due to reduced organ perfusion, leading to accumulation of the drug. Pharmacodynamic interactions between different drugs may also conceivably result in potentiation; there are indications that opioids, even in small doses, can enhance the hypnotic effect of benzodiazepines [14]. These interactions might result in oversedation if the potentiation of one drug by another is not taken into account.

Very few data are available on the value of the BIS in assessing depth of sedation in ICU patients. Shah et al. [9] found a good correlation between the Ramsay sedation score and the BIS. Although they did not control for the type and timing of medications given to their patients, they found that a maximal Ramsay sedation score of 6 corresponded with a mean BIS of 61.7 ($\pm$ 3.1). It can therefore be concluded that BIS values below this threshold of 60 could possibly reveal the presence of unnecessary deep sedation, resulting in the appearance of side-effects. In this study, we sought to detect patients at risk of oversedation, namely those with a maximal Ramsay sedation score. We observed a wide range of BIS in the patients studied, with almost half of them having an unexpectedly low BIS of around 30 and two having a mean BIS of 15. In all the patients, the Ramsay sedation score before starting the measurements was 6 and did not change during the measurement period. It can be argued that no control (either internal or a control group) was established and that the sedation regimen was not changed during BIS measurement to define different levels of sedation, but this was not the purpose of the study. We aimed at observing objectively a clinical situation, not at providing appropriate sedation or avoiding oversedation, or at titrating sedation against BIS. Patients were included as randomly available in the ICU. We suggest that a wide range of potential oversedation exists in clinically well-sedated patients. So more research is needed to correlate BIS with levels of oversedation.

No correlation was found between BIS and organ failure (renal and/or liver); a very low average BIS of 15 was found in two patients receiving continuous renal replacement therapy. Also, no correlation was found between the patients' average BIS and duration of sedation or dosages of morphine and midazolam, as shown in Figs. 2, 3 and 4, respectively. We therefore believe that an objective measurement of depth of sedation, (e.g. BIS) should be implemented to guide the sedation regimen.

In conclusion, referring to the initial data on BIS monitoring in ICU patients [9], and to observations made during anaesthesia, we advocate a BIS of around 50 to 60 as correlated with a maximal Ramsay sedation score of 6. All patients having a mean BIS below this threshold level could have been at risk of oversedation. The Aspect A-1000 EEG monitor processed a high quality signal during the measurements. The BIS might be an accurate method for assessing and controling sedation in ICU patients. To date, however, there are no data demonstrating that these cerebral function-monitoring devices, when used to assess depth of sedation, significantly alter patients' outcomes. But the risk of non-invasive cerebral function monitoring to the patient is non-existent, and potential benefits, at least theoretically, are quite possible. The objective of this study was to test the feasibility of the BIS during ICU sedation. Since this is a preliminary study, more work is required to validate the technique in this group of patients and in those less sedated.

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