Determination of loss of consciousness: a comparison of clinical assessment, bispectral index and electroencephalogram: An observational study

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Determination of loss of consciousness

A comparison of clinical assessment, the bispectral index and EEG

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Running title: Comparison of clinical assessment, BIS and EEG

Abstract

BACKGROUND Computer-processed algorithms of encephalographic signals are widely used to assess the depth of anaesthesia. However, data indicate that the bispectral index (BIS), a processed electroencephalography monitoring system, may not be reliable for assessing the depth of anaesthesia.

OBJECTIVE The aim of this study was to evaluate the ability of the BIS monitoring system to assess changes in the level of unconsciousness, specifically during the transition from consciousness to unconsciousness, in patients undergoing total intravenous anaesthesia with propofol. We compared BIS with electroencephalogram (EEG), and clinical loss of consciousness (LOC) defined as loss of verbal commands and loss of a patient's eyelash reflex.

DESIGN This was an observational cohort study.

SETTING University Hospital Linköping, University Hospital Örebro, Finspång Hospital and Kalmar Hospital, Sweden from October 2011 to April 2013.

PATIENTS Thirty-five ASA I patients aged 18 to 49 years were recruited.

INTERVENTIONS The patients underwent total intravenous anaesthesia with propofol/remifentanyl for elective day-case surgery. Changes in the patients' clinical levels of consciousness were assessed by BIS and compared with assessment of stage 3 neurophysiological activity using EEG. The plasma concentrations of propofol were measured at clinical loss of consciousness (LOC) and 20 and 30 minutes after LOC.

MAIN OUTCOME MEASURES The primary outcome was measurement of BIS, EEG and clinical LOC.

RESULTS The median BIS value at clinical LOC was 38 (IQR 30–43), and the BIS values varied greatly between patients. There was no correlation between BIS values and EEG stages at clinical LOC ($r = -0.1$, $p = 0.064$). Propofol concentration reached a steady state within 20 minutes.

CONCLUSION There was no statistically significant correlation between BIS and EEG at clinical LOC. The results suggest BIS monitoring is not a reliable method for determining LOC.

CLINICAL TRIALS REGISTRY This trial was not registered because registration was not mandatory at the time of the trial.

Keywords: PROPOFOL, EEG, BIS, DEPTH OF ANAESTHESIA.

Introduction

Anaesthetists use monitors to measure and control the depth of anaesthesia. Two of the most commonly used monitoring systems are electroencephalographic state entropy (SE) and bispectral index (BIS). Both systems measure the effect of an anaesthetic agent on neurophysiological activity in the frontal cortex. The BIS system, which has been available since the mid-1990s, is a composite of different electroencephalogram (EEG) processing techniques, including power spectral analysis, bispectral analysis and time domain analysis. The EEG signal is converted by mathematical analyses to a numerical value between 0 (isoelectric EEG) and 100 (fully awake). The BIS value of a moderately sedated patient is 80, and the ideal BIS value for surgical anaesthesia is between 60 and 40.¹ Burst suppression should correlate with a BIS value below 20.²

The National Institute for Clinical Excellence (NICE) recommends that monitors be used to measure depth of anaesthesia in patients with a higher risk of awareness or excessively deep anaesthesia and in all patients receiving total intravenous anaesthesia.³

Studies have shown that monitoring consciousness can lead to earlier recovery due to a reduction in drug consumption. In addition, some studies indicate that BIS monitoring reduces the risk of intraoperative awareness.^{4,5}

However, more recent and larger studies have not been able to reproduce these results, finding that BIS does not further reduce awareness as well as measure end-tidal anaesthetic agents.⁶ This was confirmed by Avidan and colleagues in 2011⁷ and by Whitlock and colleagues,⁸ who also found that BIS correlates poorly with end-tidal concentrations. Others had similar findings with other monitors.⁹ Furthermore, data indicate that processed EEG monitoring systems may not be suitable for assessing unconsciousness. With isoflurane-based anaesthesia, a BIS value of 70 is correlated with a 50% probability of unconsciousness, while the same BIS value in a patient anaesthetised with propofol is correlated with a 15% probability of unconsciousness. The usefulness and cost-effectiveness of depth of anaesthesia monitoring has, therefore, been questioned.³

The aim of this study was to evaluate the reliability of BIS monitoring for assessing changes in a patient's level of consciousness, specifically during the transition from consciousness to unconsciousness, in patients undergoing total intravenous anaesthesia with propofol/remifentanyl. BIS was compared to the golden standard for assessing neurophysiological activity in the brain, continuous multiple-lead electroencephalogram and to clinical loss of consciousness (LOC).

Methods

This study was approved by the Regional Ethics Committee University Hospital in Linköping, Sweden on 6 October 2008 (M184-2007, Chairperson Professor C. Dabrosin). Written informed consent was obtained from all participants. The study group was comprised of 35 ASA I patients aged 18 to 49 years old with body mass indexes (BMIs) of 20 to 30. The patients were scheduled for day-case surgery under general anaesthesia at Linköping University Hospital, Finspång Hospital and Kalmar Hospital between 5 October 2011 and 16 April 2013.

Patients with central nervous system disorders, a history of smoking, psychiatric diseases, alcohol or drug abuse, analgesic use within 12 hours prior to surgery, pregnancy or allergies to soy beans or peanuts were excluded.

All patients received paracetamol and/or a nonsteroidal anti-inflammatory drug (NSAID) prior to induction. No other premedication was administered. A peripheral venous catheter was inserted into the forearm. Standard monitoring, including pulse oximetry, non-invasive blood pressure, three-lead electrocardiography and capnography, was performed. A second peripheral IV line was used to collect blood samples during the anaesthetic period.

Bispectral monitoring and analysis:

Following preparation of the skin with alcohol, a BIS sensor was placed on the forehead according to the manufacturer's instructions. The depth of anaesthesia was registered as BIS values (Aspect BIS 14, Aspect™ Medical Systems, Inc., Norwood, USA) at the time of clinical LOC.

Electroencephalographic monitoring and analysis:

Electroencephalogram recordings were performed on a Nicolet One Neurodiagnostic system (Viasys, CareFusion Inc., San Diego, USA). A bipolar montage of the electrodes F3–T3 and F4–T4-6 electrodes in total—was used. Electrode impedance was less than 10 kΩ and the low-pass filter was set at 70 Hz. All recordings were later analysed by the same clinical neurophysiologist who was blinded to the events at the time of surgery (when the anaesthetic was injected and when signs of clinical anaesthesia were confirmed). The EEG was manually scored in 10-second epochs and classified into five different stages: Stage 1: awake; stage 2: paradoxical excitation, dominating beta activity (indicating the first effect of the anaesthetic) during at least 50% of the recording time in three 10-

sec. epochs; stage **3**: dominating delta activity (frequency 1–3 Hz) (anaesthetic state) during at least 50% of the recording time in three 10-sec. epochs; stage **4**: dominating sub-delta activity (<1 Hz) during at least 50% of the recording time in three 10-sec. epochs; and stage **5**: first instance of a burst suppression pattern.¹⁰ The longest silent period during the burst suppression pattern was calculated and noted.

The EEG ran for 20 minutes.

Anaesthetic method:

Following preoxygenation and during continuous EEG and BIS monitoring, anaesthesia was induced with 10 mg/mL of propofol (Propofol Lipuro™ B. Braun AG, Melsungen, Germany) and 50 µg/mL of remifentanil (Remifentanil Actavis™, Elaiapharm, Valbonne, France)

To obtain constant effect-site concentrations, the infusions of propofol and remifentanil were administered by two computer-controlled infuser systems: Alaris TIVA 1000 (LB 0029 ISS4) in Finspång/Linköping, and Perfusor Space, Braun, in Kalmar. The effect-site concentrations of propofol and remifentanil were estimated using the three-compartment pharmacokinetic models developed by Schneider and Minto, respectively.^{11, 12} The estimated effect-site concentration during induction was set to 6 µg/mL for propofol and 6 ng/mL for remifentanil.

Clinical LOC was determined based on the disappearance of a patient's eyelash reflex. During induction, the patients were repeatedly (every 15-30 sec) asked to open their eyes. When there was no response to auditory commands, the eyelid reflex was tested. The time of clinical LOC was defined as the moment when patients did not respond to either stimulus.

All patients received a laryngeal mask and were mechanically ventilated.

Blood samples for the plasma concentration of propofol were obtained at clinical LOC and at 20 and 30 minutes after clinical LOC. At these points, BIS values and EEG signs of anaesthetic depth were recorded.

Neurophysiological activity was monitored by EEG and BIS during the first 30 minutes of anaesthesia. The attending anaesthetist and anaesthetic nurse were blinded to the BIS values and EEG recordings.

All patients received bolus doses of morphine or fentanyl at the end of surgery prior to discontinuation of anaesthetic drugs.

The following data were documented: age, BMI, systolic and diastolic blood pressure, times of clinical LOC, induction doses and total drug doses for propofol and remifentanyl, BIS values at the time of clinical LOC and the durations of anaesthesia and surgery. S-albumin was also analysed.

Plasma concentration of propofol:

Blood samples for analysing the plasma concentration of propofol were frozen at -70°C. The plasma concentration of propofol was analysed using a validated liquid chromatography method on a Nova-pak C₁₈ column (39mm x 150mm). Isocratic elution was performed using acetonitrile and a sodium acetate buffer (55:45 v/v) at a flow rate of 1.1 mL/min. Propofol was detected using fluorescence (with excitation and emission wavelengths of 276 and 310 nm, respectively), and quantification was performed using a calibration curve in plasma between 150 and 10,000 ng/mL. The intra- and inter-batch accuracy and precision were between 97 and 105% and below 12%, respectively.

Statistics:

The significance of the relation between BIS values and EEG patterns was assessed using a Spearman correlation analysis. A *p*-value lower than 0.05 was considered statistically significant. All graphs were made using Statistica software (version 13.1, Stat Soft. Inc., Texas, USA) and Microsoft Excel.

Results

Patients:

A total of 41 patients were enrolled in this study, which took place from 5 October 2011 to 16 April 2013. Four patients were excluded due to unreadable EEG registrations, and two were excluded due to problems with time synchronization between the monitors. Thus, a total of 35 patients were considered in the final analysis. Fifteen patients (43%) were men. The mean age was 33 ± 9.6 years, and the mean BMI was 24 ± 4 . The median time from start of anaesthesia to EEG stage 3 (delta activity) was 3 minutes, and the median time to clinical LOC was 4 minutes. The median difference between EEG delta activity and clinical LOC was 1 ± 4 minutes (see Supplemental Table 1). One patient received ephedrine due to a drop in blood pressure during induction. The baseline characteristics of the included patients are shown in Table 1.

Analysis of plasma propofol concentrations:

The plasma concentrations at clinical LOC varied, ranging from 1787 to 15134 ng/mL (6803 ± 3543 ng/mL). The propofol concentration in venous plasma reached a steady state within 20 minutes, as indicated by minor changes in intra-individual changes in concentration (Table 1).

Analysis of bispectral monitoring:

A large proportion of patients had low BIS values at the induction of anaesthesia. Fifty-four per cent of the patients had BIS values below 40 at clinical LOC, with a median of 38 (IQR 30-43) and a range from 16 to 50 (Fig 1). At EEG stage 3, BIS values had a wide range (30-97), with a median of 53 (IQR 41-69) (Fig 2). The median BIS value at baseline was 97 (IQR 95-98, range 93-99), beta activity 95 (IQR 71-97, range 24-98), subdelta activity 37 (IQR 30-44, range 16-94) and at burst suppression 25.5 (IQR 23-29, range 18-45).

Analysis of continuous EEG monitoring:

EEG was registered during anaesthesia with the BIS values for all patients. The EEG recordings for all 35 patients were readable and lacked artefacts.

At clinical LOC, one patient (3%) was at EEG stage 2, fifteen patients (43%) were at EEG stage 3, thirteen patients (37%) were at EEG stage 4 and six patients (17%) were at stage 5 (Fig 3).

Comparison:

There was no statistically significant correlation between the BIS value and EEG stage at clinical LOC ($r = -0.1$, $p = 0.064$) (Fig 1).

Discussion

This study aimed to assess the depth of anaesthesia in 35 ASA I patients. The patients underwent total intravenous anaesthesia with propofol and remifentanyl applied through target-controlled infusion for elective day-case surgery.

There was no correlation between anaesthetic depth, as measured by BIS values, and clinical LOC. The BIS value at clinical LOC was lower than 38 (IQR 30-43) in 54% of patients. At clinical LOC, there was no correlation between BIS and EEG values. These results lead to uncertainty in the ability of BIS values to measure anaesthetic depth. Clinical LOC lags 1 minute behind LOC at EEG stage 3.

The depth of anaesthesia is of great importance for patients. Much research has been done on awareness. A wide variety of rates of awareness have been reported, although large studies have reported an incidence of 1–2:1000–15 000.¹³⁻¹⁵ Anaesthesia is associated with postoperative dysfunction (POCD), especially in elderly patients, but there is no evidence that deep anaesthesia is associated with POCD.^{16, 17} However, in 2005 Monk and colleagues found that low blood pressure and deep anaesthesia are independently associated with increased postoperative mortality.¹⁸ In addition, accumulated time with low BIS values is an independent predictor of negative postoperative outcomes.^{19, 20} Sessler and colleagues have also shown an increased risk of mortality when low values of MAP, BIS and MAC occur simultaneously, called a triple low state.²¹ However, recent studies could not find an association between a triple low state and postoperative mortality.^{22, 23} In our study, we found low BIS values in combination with rather high induction doses of propofol. However, we found only one drop in blood pressure during induction in our ASA I patients.

In a prior pharmaco-genetic study, we investigated the reason for the large inter-individual variation in plasma concentrations of propofol at clinical LOC.²⁴ However, the pharmacokinetic variation in propofol could not be explained by polymorphism in metabolizing enzymes or receptors.

Other studies have demonstrated that BIS values correlate well with increasing propofol dosages, even if BIS levels at induction are lower than expected.²⁵ In 2013, Martín-Mateos and colleagues showed that BIS values fluctuate around an index of 50 and that this fluctuation varies among patients.²⁶ In our study, approximately 50% of patients demonstrated low BIS values, and in five of these patients, the EEG showed a burst suppression pattern, which signifies overly deep anaesthesia. The mean induction dose of propofol was 3.1 mg/kg, which is higher than usual and could be due to an absence of premedication or variability in the determination of clinical LOC.

There is a time delay for withdrawing blood for propofol plasma concentrations, both in this study as well as in our previous studies. This might affect the pharmacokinetics and pharmacodynamics. However, in this study we only evaluated the plasma concentration and the aim was not to do a PK-

PD models since this has already been published by several research groups (A two-compartment effect site model describes the bispectral index after different rates of propofol infusion.²⁷

Despite the need to assess the depth of anaesthesia and achieve a safe, balanced anaesthetic depth, there is still no clinical monitoring system that measures anaesthetic depth in a safe and reliable way.²⁸ This might be because such a measurement is influenced by too many confounding factors, which provides an even greater reason to continue studying this area. In this study, clinical LOC was based on patients' responses to verbal commands and eyelash reflexes. The patients were repeatedly asked during induction to open their eyes. Our results show a delay of clinical LOC of 1 ± 4 min from EEG stage 3, which is the stage at which surgical anaesthesia takes place. This delay occurs because it takes time to evaluate patients' auditory responses and eyelash reflexes. Beyond the usual clinical signs of LOC, LOC can be determined by the ability to place a laryngeal mask.²⁹ Ryu and colleagues also showed that no patient needed more than 0.3 µg/kg of remifentanyl for a successful laryngeal mask insertion. In our study, a minimum of 0.31µg/kg of remifentanyl was administered before clinical LOC.

Prior studies found large inter-individual variations in BIS values measured at clinical LOC in healthy individuals.³⁰ Kaskinoro and colleagues described the difficulties of monitoring unconsciousness using an anaesthetic depth monitor applied to the forehead.²⁹ The thalamus, which is not reflected in BIS values, is involved in the regulation of consciousness.³¹ Moreover, muscle activity can cause the EEG patterns in the BIS monitor to tend towards higher values, resulting in higher BIS values for patients that are still unconscious and lack muscle relaxant.^{32,33} No neuromuscular blockades were used for the patients in our study, which could contribute to muscle interferences and, consequently, unreliable BIS values.

In a recent study, a large variation was found among EEG patterns measured at clinically evaluated LOCs. The EEG patterns varied from beta activity to suppression bursts.²⁴ Some anaesthetics, including propofol, induce CNS excitation during the anaesthetic initiation phase with increased oscillatory activity in the higher beta frequency bands (12.5–25 Hz) and decreased activity in slower frequency bands (3.5–12.5 Hz).³⁴ This state is marked by a lack of inhibition and a loss of both motor and affective control.³⁵ When patients are more deeply sedated, EEG patterns become slower with increased delta (1–3 Hz) and sub delta (<1 Hz) activity. In some instances, burst suppression patterns also develop.³⁶ Low frequency EMG signals may simulate high EEG signals associated with being awake and superficial anesthesia (ca 30Hz).³⁷ However, the BIS algorithm includes a reduction in the impact of EMG contamination, both in sedation ranges and anesthesia and a false elevation of BIS is highly unlikely.

The induction phase of propofol is rapid and clearly visible on the EEG as faster beta frequencies. However, the slower theta and delta waves emerge gradually as sedation deepens and are highly variable between patients during and after LOC.^{38, 39}

In this study, EEG activity was reduced with clinical LOC. However, there was no statistically significant correlation between EEG and BIS values. The poor correlation could be explained by different values of BIS depending on the spectral decomposition of the waves. At clinical LOC, 54% of patients had BIS values below 40, and the majority of patients had BIS values lower than 45 at 20 and 30 minutes after clinical LOC. The optimal BIS value for safe anaesthesia is between 40 and 60.¹ This means that deep anaesthesia was reached in more than 50% of our patients. However, deep anaesthesia could not be verified by EEG.

Despite the fact that EEG is the golden standard for monitoring brain activity, it is not fully clear how EEG algorithms can be used to determine anaesthetic depth. Moreover, even if the NICE recommends anaesthetic depth monitors, there are still many unanswered questions about the reliability of BIS monitoring.³

Limitations:

This study was small, which made it difficult to draw any definite conclusions. Arterial plasma concentrations of propofol might be more appropriate than venous concentrations and this could explain the somewhat higher concentration of propofol.⁴⁰ However, we had no ethical approval for an arterial line.

Another limitation is that most parameters such as BIS, EEG patterns, clinical LOC are dependent on a time-delay and therefore the response of the parameter to physiological unconsciousness cannot be registered immediately. If this time delay is different between the variables this can become a confounding factor.

Conclusions:

There was no statistically significant correlation between BIS value and EEG at clinical LOC. Our findings suggest that BIS monitoring may not be reliable and is in need of further development.

Declaration of interests:

No conflicts of interest are declared.

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Author's contribution

E-L.Z.: Study design, patient recruitment, data collection, data analysis, writing the first draft of the paper

C.E.: Study design, patient recruitment, data analysis, writing the first draft of the paper

H.G.: Study design, data analysis, writing the first draft of the paper

S.V.: Study design, data analysis, writing the first draft of the paper

M.V.: Study design, data analysis, writing the first draft of the paper

M-L.L.: Patient recruitment, data collection, data analysis, writing the first draft of the paper

A.O.: Study design, patient recruitment, data analysis, writing the first draft of the paper

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Figures

Figure 1. The BIS value at clinical LOC, showed no correlation with the EEG, based on Spearman's analysis.

Figure 2. There was a large variation in the BIS values at EEG stage 3. The median BIS value was 53 (IQR 41-69, range 30-97), which is defined as an anaesthetic state with dominating delta activity. The median BIS value at baseline was 97 (IQR 95-98, range 93-99), beta activity 95 (IQR 71-97, range 24-98), subdelta activity 37 (IQR 30-44, range 16-94) and at burst suppression 25.5 (IQR 23-29, range 18-45).

Figure 3. An example of the EEG pattern at LOC as judged by the clinical signs of the patients investigated (n=35). * First effect of the anaesthetic. ** Three out of four stages of the maintenance phase of the anaesthetic are noticed. Adapted from Brown and colleagues.¹⁰

Table 1. Baseline characteristics of the enrolled patients

Patients (No.)	35
Male (%)	43
Age (year)	33 ± 9.6
Weight (kg)	72.9 ± 13.5
Height (cm)	173,6 ± 10.5
BMI	24 ± 3
Albumin (g/L)	43,2 ± 3,5
Induction dose of propofol (mg/kg)	3,1 ± 1,1
Propofol plasma concentration at LOC (ng/mL)	6803 ± 3543
Propofol plasma concentration after 20 minutes (ng/mL)	3174 ± 1109
Propofol plasma concentration after 30 minutes (ng/mL)	3119 ± 1702

Baseline data presented as mean values ± standard deviations.