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Response of bispectral index to neuromuscular block in awake volunteers†

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Abstract

Background: The bispectral index (BIS) monitor is a quantitative electroencephalographic (EEG) device that is widely used to assess the hypnotic component of anaesthesia, especially when neuromuscular blocking drugs are used. It has been shown that the BIS is sensitive to changes in electromyogram (EMG) activity in anaesthetized patients. A single study using an earlier version of the BIS showed that decreased EMG activity caused the BIS to decrease even in awake subjects, to levels that suggested deep sedation and anaesthesia.

Methods: We administered suxamethonium and rocuronium to 10 volunteers who were fully awake, to determine whether the BIS decreased in response to neuromuscular block alone. An isolated forearm technique was used for communication during the experiment. Two versions of the BIS monitor were used, both of which are in current use. Sugammadex was used to antagonise the neuromuscular block attributable to rocuronium.

Results: The BIS decreased after the onset of neuromuscular block in both monitors, to values as low as 44 and 47, and did not return to pre-test levels until after the return of movement. The BIS showed a two-stage decrease, with an immediate reduction to values around 80, and then several minutes later, a sharp decrease to lower values. In some subjects, there were periods where the BIS was <60 for several minutes. The response was similar for both suxamethonium and rocuronium. Neither monitor was consistently superior in reporting the true state of awareness.

Conclusions: These results suggest that the BIS monitor requires muscle activity, in addition to an awake EEG, in order to generate values indicating that the subject is awake. Consequently, BIS may be an unreliable indicator of awareness in patients who have received neuromuscular blocking drugs.

Clinical trial registry number: ACTRN12613000587707.

Key words: measurement techniques, spectral analysis; monitoring, depth of anaesthesia; monitoring, electroencephalography

Editor's key points

- The influence of electromyographic activity on the bispectral index (BIS™) monitor of the adequacy of anaesthesia was evaluated.
- In awake volunteers paralysed with suxamethonium or rocuronium, BIS declined to values consistent with general anaesthesia.
- The BIS, which is based on a proprietary algorithm, is an unreliable indicator of general anaesthesia or awareness with concomitant neuromuscular block.

Neuromuscular block is implicated in the majority of instances of unintended awareness during general anaesthesia, an experience that frequently results in severe and ongoing psychological symptoms.[1–3] The bispectral index (BIS™) monitor (Covidien, Boulder, CO, USA [previously Aspect Medical Systems, Norwood, MA, USA]) is widely used to assess the level of hypnosis during general anaesthesia involving neuromuscular block.[4] In 2003, however, one small study showed that the BIS decreased in fully awake subjects when neuromuscular blocking drugs (NMBDs) alone were administered, to levels that suggested anaesthesia.[5] This was concerning, because it implied that the BIS

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monitor relied upon muscle activity (electromyogram: EMG) to detect awareness, rather than brain activity (EEG). In the 10 years since, although many studies using this device have been published, this finding has been neither replicated nor refuted.

The BIS monitor is a quantitative EEG device that uses a proprietary algorithm to analyse the electrical signal derived from a frontal electrode array to generate a number between 0 and 100; the 'BIS'. Values >80 indicate that the patient is awake, while values between 60 and 80 indicate sedation such that the patient may respond purposefully to stimulus. Values between 40 and 60 are thought to reflect a level of unconsciousness suitable for surgery.[6 7]

Studies exploring EMG and BIS in anaesthetized patients have shown that increased EMG activity increases the BIS. When EMG activity decreases, BIS also decreases regardless of whether it is a result of more anaesthetic agent or NMBDs alone.[8–15] Given that the patients in these studies were known to be anaesthetized, this has been interpreted to mean that the EMG is simply 'noise' that interferes with the BIS algorithm causing it to be 'falsely elevated'.[12–16] However, without clear evidence of how the BIS responds to the EMG in awake subjects, this conclusion is premature. It may be that the EMG in fact plays a more fundamental role in the BIS algorithm.

Neuromuscular blocking drugs used alone have no appreciable effect on conscious state, but they do eliminate EMG activity;[17–19] therefore, they offer a direct way to examine the response of the BIS to EMG changes in subjects who are unequivocally conscious. In addition, the conscious subject with neuromuscular block is exactly the situation that an awareness monitor must identify accurately in order to be effective.

We tested whether the BIS decreases in awake volunteers in response to neuromuscular block alone using suxamethonium or rocuronium. Antagonism of rocuronium with sugammadex induces a rapid return of muscle function, and we predicted that any decrease in BIS would return to baseline levels over a similar time.

Methods

After approval from our human research ethics committee, we recruited 11 unpaid volunteers. Written informed consent was obtained to take part in two experiments; the first using suxamethonium, and the second, on a separate occasion, using rocuronium.

Inclusion criteria were that subjects were anaesthetists, of ASA physical status I or II, aged 25–60 yr. Exclusion criteria included BMI >25 kg m^{-2}, gastro-oesophageal reflux, signs of a difficult airway, claustrophobia, or any anxiety disorder. The study was conducted in a fully equipped operating theatre with three-lead ECG, pulse oximetry, capnography, and non-invasive blood pressure monitoring. The subjects were fasted. An i.v. cannula was inserted in the left cubital fossa, and a BIS-xp electrode was placed on each side of the subject's forehead. One electrode was connected to a BIS Vista monitor (2013; BISx Revision 1.15, BIS Engine 4.1) and the other to a BIS A2000 monitor (2003; System Revision 3.30, BIS Engine 1.25). The default BIS smoothing rate of 15 s was selected on both monitors. A conventional 22-channel scalp EEG was also recorded (Compumedics Profusion EEG 4, Melbourne, Victoria, Australia) with electrodes placed in accordance with the international 10–20 system.

After checking electrode impedance, an EEG with closed eyes was recorded for 3 min, and the subject was pre-oxygenated by face mask. A padded cuff on the right upper arm was inflated to 300 mm Hg, and isolation of the forearm was confirmed by disappearance of the radial pulse.[20] The subject then opened their eyes, and suxamethonium 1.5 mg kg^{-1} i.v. was administered. After fasciculations had ceased, ventilation was commenced via face mask to a target end-tidal P_{CO_2} of 35 mm Hg, with tidal volumes of 7–10 ml kg^{-1}. Each minute, the subjects were asked to respond with their isolated forearm, using pre-arranged hand signals, to confirm conscious state, request any changes to ventilation, or indicate any distress, at which point anaesthesia would be induced with a 'rescue dose' of propofol 2 mg kg^{-1} i.v. Failure to respond would be treated as loss of the integrity of the isolated forearm and the 'rescue dose' given. Once ventilation was established and the subject was comfortable, cognitive function was assessed every 2 min by a simple arithmetic problem (e.g. 'What is 42 plus 9?') to be answered with hand signals. Each subject was also told a brief story that contained five key facts for later recall (e.g. '3 weeks ago, I went for a drive on the tablelands. I went to Lake Barrine and I fed a bush turkey').

The data from both BIS monitors were downloaded to a personal computer at 1 s intervals via serial port and included BIS, BIS-EMG, the signal quality index (SQI) and the suppression ratio (SR). Both BIS monitor screens were recorded on video, and all data were synchronized to the nearest second.

The rocuronium experiment was conducted on a separate occasion, at least 2 weeks later. Rocuronium 0.7 mg kg^{-1} was administered i.v., and neuromuscular block was continued for as long as the subject was able to tolerate the discomfort of the isolated forearm or until they had difficulty communicating because of paraesthesia or muscle weakness. The rocuronium was antagonized with sugammadex 3 mg kg^{-1} i.v. if >15 min had elapsed, or 6 mg kg^{-1} i.v. before that time. After the first two subjects experienced discomfort because of pharyngeal secretions, the remainder were premedicated with glycopyrrolate 200 mcg i.v. 30 min before the experiment.

Neuromuscular block was assessed clinically by movement of the left hand to command and electronically with the BIS-EMG parameter. The BIS-EMG parameter is a logarithmic scale of total power in the 70–110 Hz range, averaged over the preceding 10 s.[21] It has a minimal value of ~25 dB, and in the awake patient it is 40–60 dB. The EMG is displayed on the BIS monitor by a bar graphic, which is absent below 30 dB;[21] however, the exact values are available via the serial port. The raw EEG downloaded from the BIS monitors was used to calculate the BetaRatio and SynchFastSlow[22 23] during the period of closed-eye recording at the start of each trial and from 1 min after the onset of neuromuscular block until recovery from suxamethonium or administration of sugammadex.

Subjects were followed up by personal interview after the experiment to assess any negative psychological features relating to their participation.

Statistical analysis

The BIS values are reported as median (interquartile range; IQR) and lowest (nadir) values. A two-tailed paired Wilcoxon signed-rank statistic was used to test for differences in nadir BIS values between the two devices and between the two drug groups. To test for systematic differences between the two monitors, a linear mixed-effects model was fitted to predict BIS Vista values from the synchronous BIS A2000 values using the lme4 package in R (version 3.0.2, R Core Team, 2014, www.R-project.org). Subjects were included as random effects, allowing model intercepts to vary between them. The BIS values from both instruments were first centred by subtracting the mean of the BIS A2000, making the intercept an estimate of the mean difference between monitors. This comparison was performed for the rocuronium trials from 4 min after the onset of clinical paralysis until administration of sugammadex. We did not perform this comparison