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Restrict relaxants, be aware, and know the limitations of your depth of anaesthesia monitor

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In this issue of the *British Journal of Anaesthesia*, Schuller and colleagues examined the effect of neuromuscular block on the EEG bispectral index (BIS) in awake subjects. The researchers induced the scenario of awake paralysis in consenting volunteers.[1] Recent data indicate that awake paralysis is one of the main factors for distress during awareness, and may be even more critical than experience of pain.[2] Patients with distress during awareness are at high risk to develop long term sequelae. This is consistent with a main mechanism for the development of post-traumatic stress disorder (PTSD), the combination of a traumatizing event and the inability to follow the flight reflex and withdraw oneself from the traumatizing situation.

As a consequence, detection of consciousness seems most important when neuromuscular blocking drugs are administered. As standard anaesthesia monitoring may not detect awareness or consciousness with paralysis, this seems a main target for specific monitoring of the effects of anaesthesia on the main target organ – the brain.

In the last decades, several monitors of the hypnotic effects of anaesthesia have been developed. These measure the EEG and calculate an (alpha) numerical index value reflecting 'depth' of anaesthesia or the hypnotic component of anaesthesia. The EEG itself measures electrical activity on the surface of the scalp. It is mainly composed from signals of the brain cortex and muscle activity (EMG). It seems plausible that EEG-based monitoring reflects activity of the main target organ of anaesthesia, the brain.

Currently, development and calculation of indices of the hypnotic component of anaesthesia are based on a probabilistic approach: various parameters, which describe characteristics of the EEG signals, are calculated from the EEG. For an anaesthesia index, these parameters are combined using different proprietary algorithms. For the development of such an index, EEGs are recorded during volunteer and patient studies. Simultaneously, the hypnotic component or the level of anaesthesia is clinically assessed. Calculated EEG data and the results of clinical assessment are stored in a database. Using statistical and mathematical (probabilistic) methods, parameters calculated from the EEG are combined to produce an index value, which corresponds to the observed level of anaesthesia.

This database-driven approach may have limitations, in particular for the detection of intraoperative wakefulness: it is very unlikely that data from an awake and paralyzed subject are included in this database. Therefore, the resulting anaesthesia index has not been trained with a dataset that contains this clinical situation, and it remains unclear whether such a situation is adequately classified by such an index.

Current EEG-based monitors analyse the EEG spectrum in a range where cortex activity and EMG activity overlap.[3] As current indices of anaesthesia are calculated with proprietary algorithms, it is unclear to which extent the index is based on analysis of brain activity and to which extent EMG parameters may contribute to an anaesthesia index (i.e. whether a proprietary index may subsequently be influenced by neuromuscular block).

It has been clarified that an index of anaesthesia can be calculated on the basis of spontaneous (EEG) or evoked (evoked potential, EP) electrical brain activity and muscle activity (EMG).[3] Even if the EMG is a surrogate measure and does not reflect activity of the main target organ of anaesthesia, the brain, it may still contain useful information. Discomfort may lead to facial muscle activity (grimacing), therefore inclusion of muscle activity into a monitor may increase the sensitivity to detect insufficient blockade of reactions to stimuli. The disadvantage of the inclusion of muscle activity is the potential dependence of an index on muscle activity to calculate an index value that indicates consciousness: neuromuscular block decreases EMG activity and this decrease may lead to a misinterpretation of neuromuscular block as (deep) anaesthesia. This pharmacologically induced decrease of muscle activity (EMG) is not related to sedative or hypnotic anaesthetic effects. Therefore, analysis of the EMG may not be a useful basis for an index of the level of anaesthesia, because neuromuscular block decreases EMG activity and this decrease may lead to a misinterpretation of neuromuscular block as (deep) anaesthesia.

For a previous version of the BIS monitor (BIS A-1000 monitor, BIS version 3.31), a small study in volunteers showed the influence of neuromuscular blocking agents on the BIS index value: with isolated forearm technique, neuromuscular block was induced in awake volunteers, and BIS decreased after administration of succinylcholine, while subjects were able to move the isolated hand to command.[4]

This study has often been cited, and subsequently the A-2000 monitor and BIS XP™ platform were released. This version of the BIS included a new sensor with an additional electrode above the eyebrow. This additional electrode was designed to identify signal contents related to muscle activity and the monitor now provides an indicator of EMG activity.

Accordingly, the manufacturer suggested that the new hardware and software had solved the problem, but in daily clinical practice, attention had been directed towards the interference of EMG and EEG signals.[5] Dahaba and colleagues tried to analyse the influence of different degrees of mivacurium-induced neuromuscular block on BIS XP™ in patients.[6] They found little influence of mivacurium when administered during propofol anaesthesia, with BIS-values between 40 and 50. This confirmed results of a volunteer study with propofol and mivacurium,[7] which did also not identify a decrease of BIS values when mivacurium was administered at baseline

BIS between 40 and 50. Both studies have in common that they analyse the influence of neuromuscular block on BIS values, which are already low after propofol administration. After propofol-induced loss of consciousness, both high frequency components of the EEG and (high frequency) EMG activity decrease. In this situation, additional neuromuscular block may not add much changes to the EEG.

Only if EMG activity is present, administration of neuromuscular blocking agents may change the index value. These changes have been observed in patients during anaesthesia[8 9] and in the intensive care unit.[10]

The clinical interpretation of this EMG influence requires caution. In many instances, the effect of EMG on BIS was treated as artifact, and the application of neuromuscular blocking agents has been used to reduce the influence of this artifact. Higher index values measured without neuromuscular blocking agent were even judged to be 'spurious',[9] and it has been suggested that BIS calculation from a signal containing EMG may lead to an 'overestimate' of index values. As the present study of Schuller and colleagues suggests, the values recorded under neuromuscular block may be spurious (i.e. the application of neuromuscular blocking agents may prevent the BIS monitor detecting awareness).

The described misreading of EMG influence arises - at least in part - from the fact that the BIS algorithm is proprietary and unknown to the clinical user: it can only be observed that EMG has an influence on BIS, but it cannot be deducted from the algorithm how much EMG contributes to BIS in general, or how much EMG contributes to calculation of low and high BIS values. The results of Schuller's study show that the influence of EMG on BIS is so high that the absence of EMG leads to BIS values representing 'surgical anaesthesia'.

As a consequence of Schuller's findings, several recommendations and guidelines should carefully be revised: BIS monitoring has been recommended in ICU-patients, in particular when neuromuscular blocking agents are administered.[11] As the present data show, this may in particular be a situation with misleading BIS values.

Despite of these limitations, EEG-based monitoring of the hypnotic component of anaesthesia, has introduced a monitor of the anaesthetic effect on the main target organ of general anaesthesia, into daily clinical practice. With the broader application of monitors of the hypnotic component of anaesthesia, EEG-based monitoring has evolved from a research method to a clinical tool. It has been demonstrated that after a brief structured training in EEG reading and practical application in the operating theatre, anaesthetists are able to estimate the BIS value from the unprocessed EEG.[12] This demonstrates the feasibility of intraoperative EEG monitoring as an integral part of anaesthesia monitoring. EEG-based monitoring allows a specific assessment of anaesthetic effects on the main target organ of anaesthesia. With the knowledge of its limitations, even the application of an anaesthesia index may be useful. But if such an index is used, it is essential to know not only its advantages, but also its limitations, to avoid misinterpretation of index values: as shown by Schuller and colleagues, neuromuscular block may mimic deep anaesthesia index values, even in awake subjects. Thus, the risk of awake paralysis is increased with possible critical consequences for the patient. Therefore, it may be useful to use an EEG-based monitor, but its usefulness under neuromuscular block is limited. This limitation is because of the use of high frequency components of the EEG and the probabilistic approach. By now, our knowledge about mechanisms behind anaesthesia-induced unconsciousness has increased and future research should focus on the development of an index, which is based on underlying mechanisms of anaesthesia-induced unconsciousness. As long as such an indicator is not available, it may be useful 'to relax, be aware, and know what you are doing',[13] but more appropriate to restrict neuromuscular block, be aware, and know the limitations of your anaesthesia hypnosis monitor.

Declaration of interest

None declared.

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ARTICLE

ARTICLE

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

for the suxamethonium trials because of the short and variable duration of the neuromuscular block and the lack of a definitive end point. To compare the variances of the two monitors, data were subdivided into 30 s intervals and the mean and variance for each interval calculated. A linear mixed-effect model was fitted to predict variance in BIS from mean BIS for each interval.

Results

Three women and eight men aged between 29 and 52 yr were recruited. Ten subjects were tested with suxamethonium and 10 with rocuronium. Two subjects repeated the suxamethonium trial for technical reasons. In one instance, both monitors failed to generate a BIS value for 20 s at the very beginning of the trial (Subject 1). In the other, one electrode failed completely on self-test at the time of fasciculations (Subject 8). Two subjects also repeated the rocuronium trial. One experienced discomfort because of excessive secretions after 8 min, and the trial was terminated with propofol. The experiment was conducted uneventfully 2 weeks later, with glycopyrrolate premedication. The other subject did not achieve complete neuromuscular block with the initial dose of rocuronium and so the trial was repeated with a higher dose (Subject 5). One subject requested trial termination during the onset of neuromuscular block with rocuronium.

In all trials, the BIS of both monitors decreased immediately after the onset of muscle relaxation and did not return to baseline levels until after clinical recovery from neuromuscular block. In some trials, the two monitors agreed closely, whereas in others there were periods where the BIS values differed by up to 15 units for several minutes. Summary data are shown in Tables 1 and 2.

Response to suxamethonium

The typical response of BIS (nine of 12 trials) was a decrease, within 15 s of fasciculations, to values between 75 and 85 (median 81, IQR 79–84). This persisted for up to 4 min, and if the subject was then still paralysed there was a second, more profound decrease to values as low as 44 (median 66, IQR 60–75). Such a 'two-stage decrease' was evident in five trials; and when it occurred, it was displayed on both monitors simultaneously (Figs 1 and 2). In four trials, recovery of muscle function occurred before 4 min had elapsed, and the BIS did not show a second decrease.

In the remaining three trials, the BIS decreased immediately after the end of fasciculations to values as low as 48, and then fluctuated until the return of muscle activity (median 67, IQR 61–73). One subject was difficult to ventilate, and manipulation of the face mask resulted in movement that was identified as EMG by the BIS monitor. During this time, the BIS rose to 85.

The lowest BIS displayed was 44 with the A2000 monitor (Subject 3) and 47 with the BIS Vista (Subjects 4 and 6). A BIS below 60 was displayed at some point in five trials with the A2000 and in seven trials with the BIS Vista. The longest continuous times below 60 were 211 s (A2000) and 91 s (Vista). This represented 76% and 25% of the total paralysis time, respectively (Fig. 2). Part of one suxamethonium trial can be seen in the video available in the Supplementary material, which can be viewed from the article in *British Journal of Anaesthesia* online.

Response to rocuronium

The response of the BIS to rocuronium was similar, with a two-stage decrease evident in seven of 10 trials characterized by a decrease to 75–85, and after 4 min a second decrease to values as low as 46 (median 73, IQR 66–77). The transition of the two-stage decrease was more gradual than with suxamethonium (Figs 3 and 4). There were values below 60 in nine trials with the A2000 monitor and in three trials with the BIS Vista. The longest continuous times below 60 were 202 s (A2000) and 55 s (Vista). The BIS Vista decreased to values of 62 or lower in seven trials.

After administration of sugammadex, the mean time to recovery of first muscle movement was 27 s (range 19–41) and to

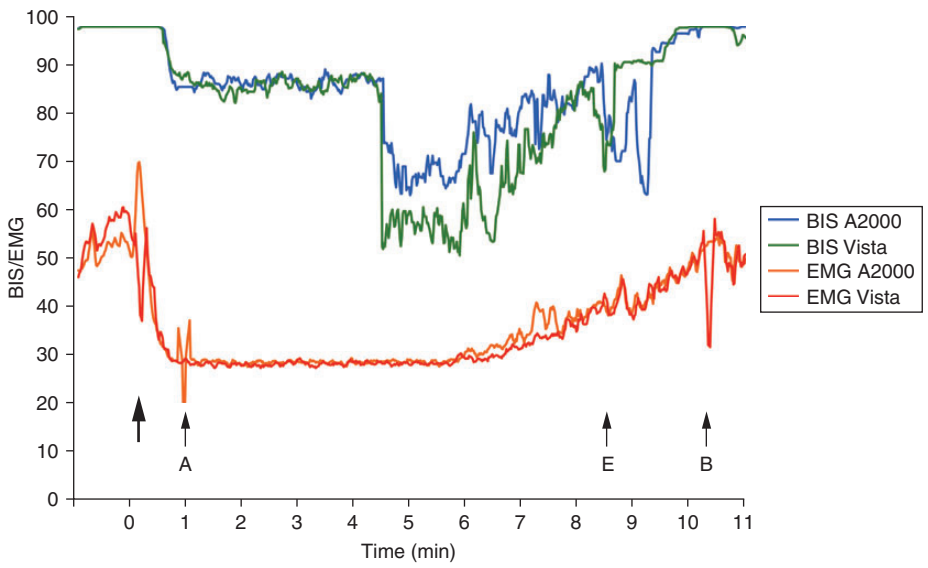

Fig 1 Bispectral index and EMG response to suxamethonium in Subject 1. Note the close agreement in EMG between the two devices. The fasciculations are evident as the sharp spike in EMG on the left (large arrow), followed by a decrease to below 30 dB within 30 s. Both BIS decreased immediately after the fasciculations, from 97 to the mid-80s. Four minutes later, there was a second sharp reduction. In 1 s, the BIS Vista decreased from 84 to 52 and the BIS A2000 from 87 to 74. The BIS Vista was below 60 for 91 s consecutively. The BIS rose again as the neuromuscular block resolved and EMG activity was detected. Eye-opening is indicated by arrow E. The M-shaped spikes in the EMG trace (arrows A and B) are BIS electrode impedance-checking signals.

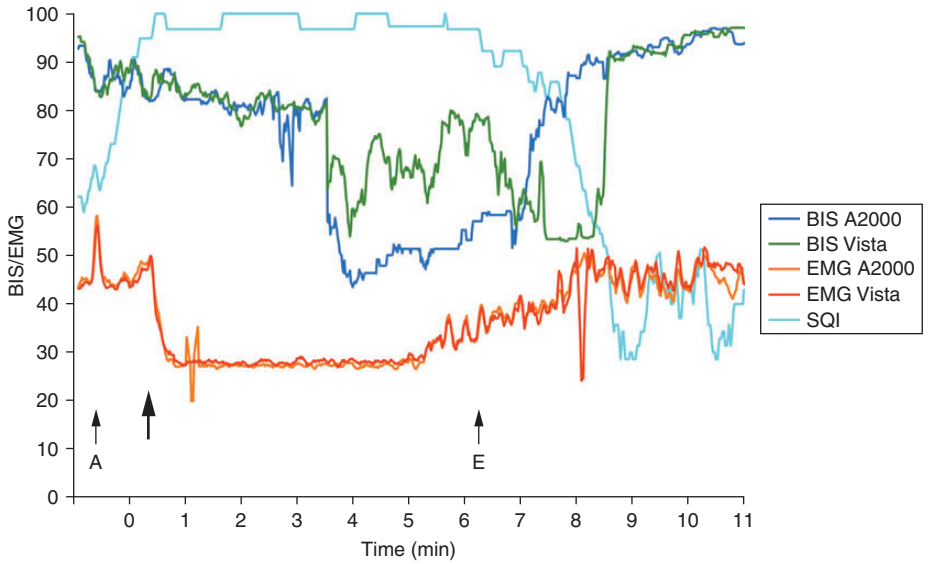

Fig 2 Bispectral index and EMG response to suxamethonium in Subject 3. The BIS on both monitors decreased to the low 80s shortly after suxamethonium administration. Several minutes later, the BIS Vista decreased sharply from 82 to 64 and the BIS A2000 from 83 to 56. The onset of the second decrease is 3 min 17 s after suxamethonium administration, but it is almost exactly 4 min after a transient increase in EMG attributable to movement of the subject's head during pre-oxygenation (arrow A). Fasciculations were minimal in this female subject (large arrow). One BIS monitor was below 60 for 3 min 31 s (A2000) and the other for 51 s (Vista). The signal quality index (SQI) increases to values above 95 soon after fasciculations, and then decreases with the return of muscle function and eye blinking. Eye opening is indicated by arrow E.

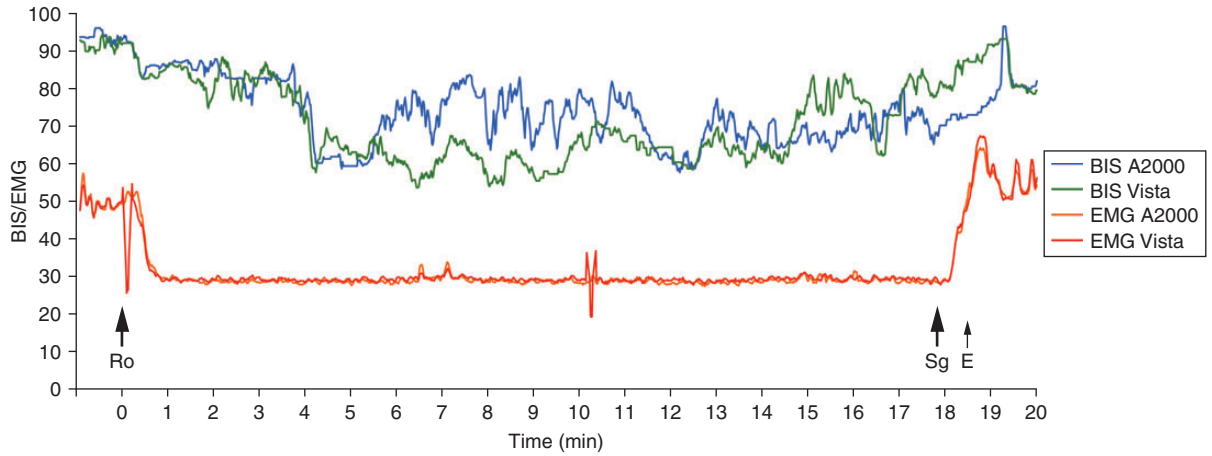

Fig 3 Bispectral index and EMG response to rocuronium (Ro) in Subject 8. After onset of neuromuscular block, the BIS decreased to values around 75–85, and ~4 min later, reduced to 58 and 60. The BIS Vista remained below 70 for most of the next 15 min and was below 60 for periods up to a minute at a time. Sugammadex (Sg) was administered at 17 min 45 s, and BIS-EMG reached 40 dB 29 s later, coincident with eye opening (arrow E).

recovery of breathing 38 s (range 26–55). The mean time to return to a BIS above 90 after sugammadex was 86 s for the A2000 (range 55–139) and 70 s for the Vista (range 39–104).

Cognitive function

All subjects were responsive to questioning during the experiment, reported that they were completely aware and felt neither drowsy nor confused. The arithmetic questions were answered with 96% accuracy. Two subjects in the suxamethonium arm were not given memory tests, one because of ongoing difficulties with face-mask ventilation and a short duration of neuromuscular block, and the other because of an oversight. The memory stories were recalled with 94% accuracy. One subject could recall only two of the key facts ('Something about a bush turkey on the tablelands'), reporting that they had been distracted at the time by an unpleasant sensation of secretions pooling in their pharynx.

Table 1 Duration of suxamethonium block, lowest bispectral index (BIS), and duration of BIS <60 or <70. *Duration of decreased BIS exceeded the duration of neuromuscular block. '–' indicates failed electrode

Subject	Duration (min:s)	Lowest BIS		BIS <60 (min:s)		BIS <70 (min:s)	
	EMG <35	A2000	Vista	A2000	Vista	A2000	Vista
1	7:17	48	49	4:07 (57%)	2:20 (34%)	8:10 (112%)*	6:38 (91%)
1	7:15	63	51		1:49 (25%)	1:26 (20%)	2:32 (35%)
2	3:58	77	77				
3	5:40	44	53	3:32 (62%)	1:23 (24%)	3:40 (65%)	3:27 (61%)
4	4:44	77	79				
5	4:44	67	47		0:46 (16%)	0:01 (0%)	1:28 (31%)
6	6:19	62	47		0:33 (9%)	1:34 (25%)	2:18 (36%)
7	5:20	59	57	0:33 (10%)	0:11 (3%)	2:53 (54%)	1:29 (28%)
8	3:05	–	49	–	0:59 (32%)	–	2:09 (70%)
8	3:08	78	74				
9	4:34	56	61	0:31 (11%)		2:18 (50%)	2:12 (48%)
10	4:13	56	61	0:09 (4%)		0:33 (13%)	0:05 (2%)

Table 2 Duration of rocuronium block, lowest BIS, and duration of BIS <60 or <70. *Incomplete neuromuscular block (see Fig. 6)

Subject	Duration (min:s)	Lowest BIS		BIS <60 (min:s)		BIS <70 (min:s)	
	EMG <35	A2000	Vista	A2000	Vista	A2000	Vista
1	15:22	51	56	7:36 (49%)	2:56 (19%)	12:21 (80%)	11:31 (75%)
2	11:14	52	61	1:10 (10%)		3:32 (31%)	2:32 (23%)
3	19:25	56	62	0:09 (1%)		6:10 (32%)	6:23 (33%)
4	17:26	69	62			0:16 (2%)	3:20 (19%)
5*	18:53	70	69			0:02 (0%)	0:37 (3%)
5	25:14	47	69	2:42 (11%)		9:08 (36%)	0:19 (1%)
6	19:53	54	62	2:28 (12%)		12:04 (61%)	3:10 (16%)
7	21:22	57	62	0:13 (1%)		5:12 (24%)	0:42 (3%)
8	08:08	56	46	0:07 (1%)	1:01 (12%)	1:20 (16%)	4:04 (50%)
8	17:36	58	54	1:05 (6%)	3:07 (18%)	7:16 (41%)	10:47 (61%)
9	20:27	54	66	1:23 (7%)		4:58 (24%)	0:05 (0%)

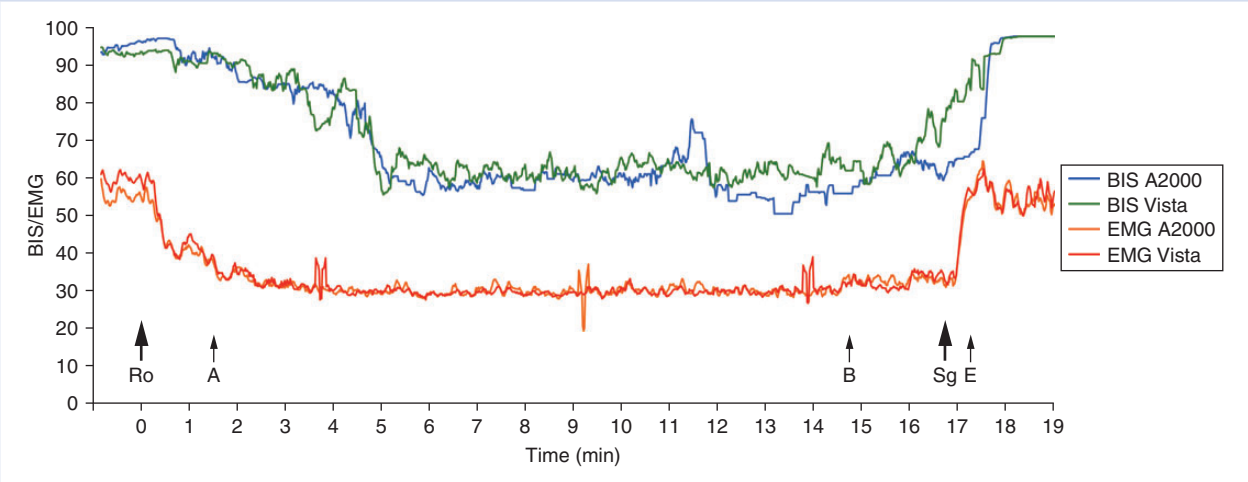

Fig 4 Bispectral index (BIS) and EMG response to rocuronium in Subject 1. Clinical paralysis was evident 90 s after administration of rocuronium (arrow A), and the two BIS monitors show close agreement for most of the experiment. At 14 min 30 s, there was a small rise in EMG and the subject reported that they were able to move their tongue slightly (arrow B). Partial diaphragm function returned at 16 min 10 s, and sugammadex was administered 30 s later. Abbreviations: Ro, rocuronium; Sg, sugammadex. Eye opening is indicated by arrow E.

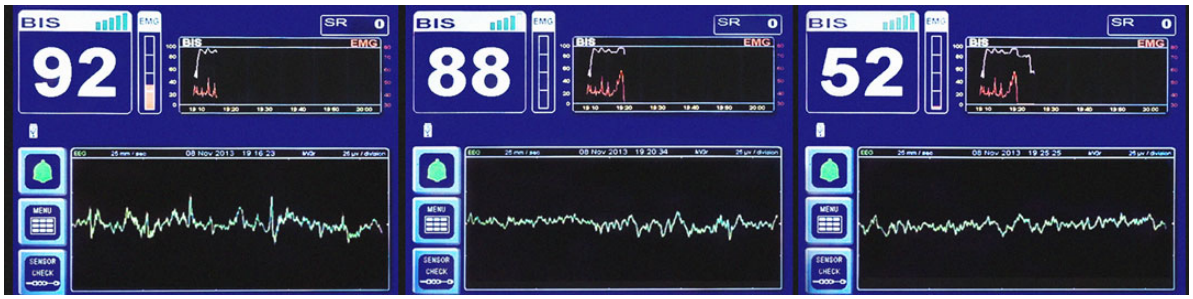

Fig 5 BIS Vista screen capture during one suxamethonium trial (Subject 1). The BIS Vista screenshots were made 3 min before, 1 min after and 6 min after administration of suxamethonium. The duration of each screen is 4 s, and the screen amplitude is +50 to −50 μV. The EEG waveform is typical of an awake subject throughout the experiment. Note the presence of EMG in the leftmost screen, where the waveform shows the characteristic high-frequency spikes of muscle activity superimposed on the underlying cortical EEG. After neuromuscular block, the EMG activity is absent but the EEG is otherwise unchanged. Examples of the multi-channel raw EEG are available in the Supplementary material.

Electroencephalogram

There was no change in raw EEG after neuromuscular block except for the absence of EMG artifact and eye movements (see Fig. 5). In all subjects, the raw EEG showed a low-amplitude, high-frequency pattern with varying degree of alpha waves, consistent with that of an awake subject with closed eyes. Examples of the multi-channel raw EEG are included in the Supplementary material.

Both the BetaRatio and the SynchFastSlow parameters decreased in all subjects after the onset of neuromuscular block. The mean BetaRatio[22] decreased from −0.19 to −0.71 after suxamethonium and from −0.14 to −0.78 after rocuronium (SEM=0.05). The mean SynchFastSlow decreased slightly from −1.75 to −1.87 after suxamethonium and from −1.53 to −1.84 after rocuronium (SEM=0.12). In the two subjects who were given propofol, the BetaRatio decreased further to minimal values of −1.5 and −1.4.

Signal quality index

In all subjects, the SQI rose after the onset of muscle relaxation and remained at levels of 90–100 until return of muscle activity (Fig. 2). In some instances, establishing adequate ventilation required manipulation of the face mask, and this movement was interpreted by the BIS monitor as either artifact or EMG. During this time, the SQI decreased until after the manipulation ceased.

Comparison of devices

There was no statistically significant difference between the intercept and zero for the model predicting BIS Vista from A2000, indicating that there was no difference in mean values ($P>0.05$, 95% confidence interval=[−0.9, 3.8]). The BIS Vista had a lower variance than the A2000 (Vista 4.6, SEM=0.32 *vs* A2000 7.3, SEM=0.57, $P<0.001$). There was no statistically significant difference in nadir BIS values between the two monitors ($W=73$, $P=0.40$) or in nadir values between the rocuronium and suxamethonium groups ($W=113$, $P=0.25$). Trials that were repeated were not included in the statistical analysis.

Subjective responses

A transient tachycardia occurred during the suxamethonium fasciculations, which resolved within 30 s (mean 110, range 82–147). All subjects developed a tachycardia of 110–120 beats min^{-1} after administration of rocuronium, consistent with its mild vagolytic properties, which persisted until after the administration of sugammadex. Sustained periods of attempted movement of paralysed limbs were associated with a further increase in heart rate to 130–140 beats min^{-1}, which has been described previously.[18]

Participants described a qualitatively different sensation to the two neuromuscular blocking agents. The fasciculations attributable to suxamethonium were painful, and the ensuing paralysis was experienced as a feeling of profound heaviness, 'as if someone had pulled the plug and drained the fluid out'. In contrast, neuromuscular block with rocuronium lacked the sensation of heaviness; the subject was simply unable to move, as if 'encased in a wetsuit made of lead'. In several subjects, any attempt to move was associated with an immediate onset of distress, which was difficult to describe but which resolved as soon as the attempted movement was abandoned. This effect appeared to be more intense with suxamethonium. No subjects reported any adverse psychological symptoms on follow-up interview.

Discussion

This study shows that in subjects who are fully conscious, neuromuscular block alone causes the BIS™ monitor to generate values suggesting deep sedation or general anaesthesia. Furthermore, the BIS does not return to baseline values until after the return of muscle activity; that is, the BIS monitor does not generate appropriate values when presented with the EEG of an awake brain, unless there is also muscle activity present. We have confirmed previous findings that neuromuscular blockade alone does not cause sedation, and that cognition remains intact [17–19]. The normal responses of the subjects during the experiment and the fact that the cortical EEG appeared awake throughout, are evidence that the BIS decrease is because of a flaw in the algorithm, rather than the result of a previously unknown effect of neuromuscular block.

The BIS was developed using a multiple-regression technique, from a database of scalp EEGs recorded during anaesthesia.[16] The signal from a frontal electrode array is used to calculate several subparameters, which are then combined, via an undisclosed algorithm, to produce the BIS index. Two of

these are the BetaRatio and the bispectral SynchFastSlow parameters, which are derived from frequencies in the 11–47 and the 0.5–47 Hz ranges, respectively.[16 22] The BetaRatio has been shown to be a sensitive indicator of the transition between consciousness and unconsciousness in subjects who have not been given NMBDs;[24 25] and it largely determines the BIS in the 60–100 range.[22 23]

At the frequencies used to calculate these subparameters, however, EMG power may greatly exceed that of the EEG. For frequencies >20 Hz, the EMG of an awake subject is between 6 and 100 times greater than their EEG.[26] With increasing sedation, the EMG power reduces, and in a deeply anaesthetized, unstimulated patient, the signal from a frontal electrode is almost entirely from the brain alone.[7 27–29] Given that the BetaRatio is calculated from these same frequencies, it would be expected that a decrease in EMG will cause a corresponding decrease in BetaRatio, which we confirmed. A system that relies on the BetaRatio to monitor the conscious state will fail when NMBDs are used, because these drugs will cause the BetaRatio to decrease, even in an awake subject.

Although the exact BIS algorithm remains proprietary, the volunteer experiments used in the development of version 3.0 of BIS have been described in some detail. These experiments used isoflurane, propofol, and midazolam to calibrate the BIS, but notably did not involve the use of any NMBDs.[30] Use of BIS in patients who have been given NMBDs may therefore be an example of using a statistically based technique in a population to which it is not applicable.

The two-stage decrease and the associated 4 min delay are unexpected findings and have several implications. It follows that the BIS at any point may be affected by an event that occurred up to 4 min earlier, which is a substantially longer time than has been previously reported,[7 22 31] and more than what is implied by the BIS technical documentation.[6 21 32] The fact that the two-stage decrease is so marked and mirrored so closely by the two BIS monitors suggests that it is because of a state change within the BIS algorithm rather than the result of a simple moving average.[22] Once the BIS has reduced to low levels, however, variations in EMG are reflected in corresponding BIS variations within 15 s, so the relationship between EMG and BIS is complex. This is most evident in the one subject with incomplete neuromuscular block (Fig. 6) and in the swift increase in BIS after antagonism with sugammadex. Whether these responses are because the algorithm is using EMG explicitly as an independent indicator of awareness or are simply attributable to its effect on subparameters such as the BetaRatio, only the manufacturers can say. Whatever the reason for the two-stage decrease and the 4 min delay, it is concerning that we are still elucidating the basic properties of this device more than 10 years after its release for clinical use.[33]

The SQI is the only displayed parameter on the BIS monitor that gives the clinician any indication of its internal reliability. The SQI is not simply a measure of the quality of electrode contact, but is the 'percentage of good epochs . . . in the last 61.5 sec', based on 'impedance data, artifact, and other variables'.[32] The BIS technical specification states that a high SQI 'indicates that the signal quality is good, *and the values are reliable*'.[32] Given that the major cause of patient-related artifact is movement, it is not surprising that the SQI will increase towards 100 when NMBDs are administered, as we found. Unfortunately, the high SQI will indicate that the BIS is at its most reliable exactly when it is performing most poorly in the aware but paralysed patient. Consequently, the SQI may be of little use as an indicator of the reliability of the BIS when a subject has been given NMBDs.

Differences between the BIS monitors

There have been a number of software changes to the BIS platform during the 10 years that separate the release of the two monitors. Documentation is lacking regarding these changes and whether they are of any clinical significance. Neither monitor was consistently superior in reporting the true state of awareness, however there were periods when the two devices disagreed by >10 units. This may reflect differences between the two monitors; but it has been shown previously that even identical BIS monitors can display markedly different values when used simultaneously on the one patient.[34]

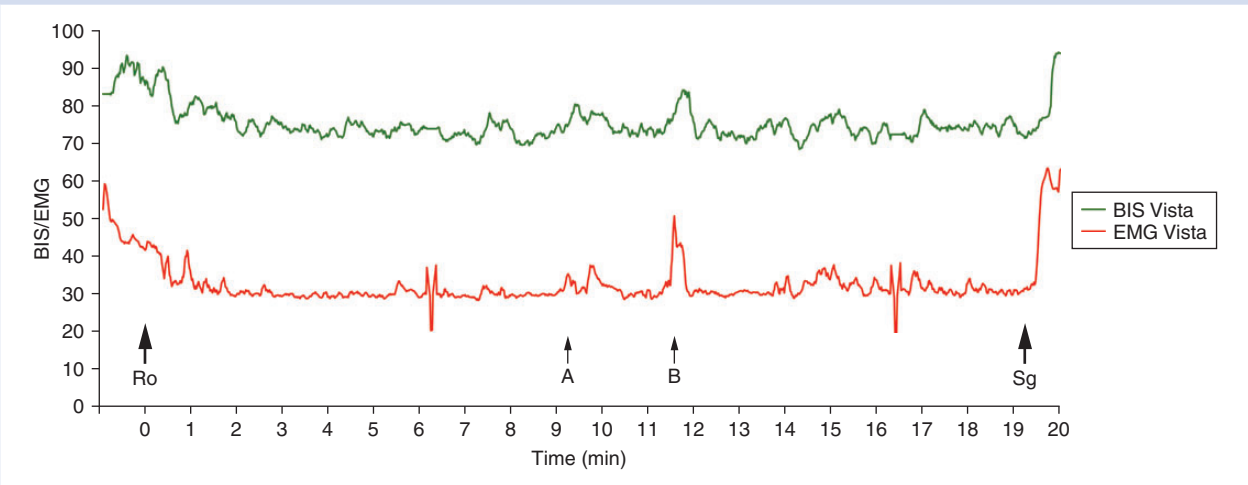

Fig 6 Incomplete neuromuscular block with rocuronium in Subject 5. The BIS and EMG response in an awake subject with incomplete neuromuscular block to rocuronium 0.7 mg kg^{-1}. For clarity, only the BIS Vista data are shown. The subject was able to slightly move their eyes, tongue, toes and forehead throughout the experiment, with noticeable 'fade'. The increases in EMG (arrows A and B) correspond to attempted movement of the eyes and forehead, with similar changes evident in the BIS a few seconds later. In this situation, muscle activity has caused the BIS to rise above 80, thus correctly indicating that the subject is awake. Abbreviations: Ro, rocuronium; Sg, sugammadex.

Limitations

This study has only a small number of subjects and so the incidence and the degree of very low BIS values may differ in the wider population. The disagreement between the two BIS monitors may be because the electrode arrays were placed on opposite sides of the head, but there is no suggestion that one side of the head is preferred. It is not possible to place two BIS electrodes on the one patient without slightly modifying the positioning of one of them, because the central electrode (Fpz) is at the common midline position; however, it is unlikely that this has a large effect, because the displacement from the optimal position was <2 cm.

Implications

These results suggest that BIS values with and without neuromuscular block are not comparable. Studies using BIS should therefore distinguish between anaesthesia that does and does not use NMBDs. Results from previous studies may need to be re-evaluated. This will be especially relevant for those studies evaluating BIS use during sedation or light anaesthesia, because the effect of the EMG on BIS will be most significant in this group.

It has been suggested that a BIS range of 60–75 is suitable for 'the end of surgery',[35 36] but our results show that if neuromuscular block is used, this range is consistent with full awareness. This is of particular relevance given the recent introduction of sugammadex, which has enabled the use of profound neuromuscular block until the last moments of surgery.

Conclusion

We have shown that BIS decreases in awake subjects in response to neuromuscular block alone, despite them having a normal, awake EEG. In some subjects, the BIS monitor reports values below 60 for minutes at a time and with transient decreases to values as low as 44. It has a delay in computation of up to 4 min. The only indicator of internal reliability of the BIS monitor, the SQI, gives falsely reassuring values during neuromuscular block. These results suggest that the BIS algorithm requires muscle activity in order to generate values indicating that the subject is awake. Consequently, the BIS may be an unreliable indicator of awareness in patients who have received neuromuscular blocking drugs.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

P.J.S. designed and conducted the study, analysed the data, and wrote the manuscript; he is responsible for archiving the study files. J.J.B. helped to conduct the study and helped to write the manuscript; he has seen the original study data and approved the final manuscript. S.N. and P.A.S. helped to conduct the study, have seen the original study data, and approved the final manuscript.

Acknowledgements

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Declaration of interest

None declared.

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Cairns Anaesthetists' Association.

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Bis: looking beyond the number

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Editor—We read with great interest the original article by Schuller and colleagues[1] in the BJA. We have anecdotally observed the numerical value of BiS to decrease upon the administration of neuromuscular blocking agents in our clinical practice. The findings of the study suggests that the decrease in BiS index value may be clinically relevant and may affect the reliability of using the BiS value as an indicator of depth of anaesthesia, particularly when neuromuscular blocking agents are used.

Interestingly, the authors commented that the raw EEG remained unchanged despite the decrease in BiS values. A previous study by Barnard and colleagues[2] investigated the feasibility of teaching practising anaesthetists to recognize changes in the frontal EEG waveform, at different stages of anaesthesia. Their results suggest that this is achievable after a brief teaching presentation. With training, the assessment of depth of anaesthesia may be augmented by the clinician's basic analysis of the changes in the frontal EEG waveform, during different phases on anaesthesia, in addition to the changes in BiS index value. Of note, the recent NAP 5 report[3] recommended the utilization of all the information available, when using a depth of anaesthesia monitor. The EEG waveform does provide additional information and its analysis may allow a more complete interpretation of anaesthetic depth, in addition of all of the other parameters currently at our disposal.

Declaration of interest

None declared.

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Response of bispectral index to neuromuscular block in awake volunteers

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Editor—We read with interest the recent study of the effects of neuromuscular blockade on the raw electroencephalogram (EEG) and bispectral index (BIS) in awake volunteers.[1] The findings were that attenuation of electromyogram (EMG) by

neuromuscular blockade resulted in BIS values as low as 44, which did not return to pre-test levels until after the return of movement. The conclusion was that BIS monitoring may be unreliable in paralyzed patients, leading to an increased risk of awareness, as the displayed BIS value is overestimating the depth of anaesthesia. The study raises several issues, which we believe should be considered before extrapolating this finding to clinical practice.

1. The volunteers did not receive noxious stimulation.

The experimental set-up does not replicate a clinical situation. During surgery BIS usually increases to values associated with awareness if a surgical or other noxious stimulus is applied, irrespective of whether neuromuscular blockade is present.

2. This observation is inconsistent with most clinical and research knowledge and experience.

A wealth of clinical experience and large clinical studies support the view that BIS monitoring does not increase the incidence of awareness in either at-risk patients or general patient populations.[2,3] In fact, it may contribute to patient safety by reducing the incidence of awareness and/or allowing lower doses of anaesthetic drugs to be administered to sensitive patients.[2–4] The authors and accompanying editorial focus on the possible risk of awareness, without mentioning the controversy over the repeated observational finding of increased mortality in vulnerable patients who are deeply anaesthetized.[4,5] Preventing excessively deep anaesthesia is another potential use for these monitors.

3. No (depth of anaesthesia) monitor is perfect.

The BIS monitor does not provide a perfect number that can be interpreted in isolation from its clinical context.[6] Learning to interpret the basic EEG trace and the effects of commonly used anaesthetic drugs can improve the utility of BIS monitoring, but no monitor based on the spontaneous EEG will reveal the full spectrum of anaesthetic drug effects on the central nervous system.[7] The experimental EEGs in the article by Schuller and colleagues[1] do not look typical of normal general anaesthesia, largely because they lack recognizable sleep spindles. These would be expected at a BIS of 50–60 during standard volatile or propofol-based anaesthesia. The index number should not be looked at in isolation from the EEG waveform and the clinical context.

Schuller and colleagues[1] have confirmed an interesting finding, but we urge caution in overinterpreting the result when clinical evidence does not support the relevance of the conclusions. Only adequately powered, patient-centred outcome studies can answer the question of the utility of such devices when used in the clinical setting. Perhaps the Editor's key point should properly read: 'The BIS, which is based on a proprietary algorithm, is an unreliable indicator of awareness with concomitant neuromuscular block in unstimulated unanaesthetised volunteers'.

Declaration of interest

The authors are on the Steering Committee of the Balanced Anaesthesia Study, a prospective, randomised clinical trial of two levels of anaesthetic depth on patient outcome after major surgery.

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To BIS or not to BIS

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The study by Schuller and colleagues[1] has elicited many reactions, including the term 'game-changer', and surely mandates a relook at commercially available depth of anaesthesia (DOA) monitors such as the bispectral index (BIS) monitor. Anaesthetic awareness with or without explicit recall has been shown to have an incidence of up to 2 per 1000 patients using the modified Brice interview. This may result in post-traumatic stress disorder, making it an important patient safety issue, which calls for standards of intraoperative monitoring in order to prevent this potentially devastating complication.[2]

As yet, no gold standard for identifying awareness exists, despite the clinical feasibility of DOA monitors having been established by identifying EEG changes in response to anaesthetic agents and clinical state alterations. The limitations of various proprietary algorithms have been recognised as reflecting a probability function of clinical state rather than actual physiological parameters.[3]

The landmark B-Aware trial demonstrated a BIS-guided reduction of awareness in at-risk adult surgical patients undergoing relaxant general anaesthesia (GA), but at a cost of $2200 per

case prevented and a number needed to treat (NNT) of 138.[4] In contrast, the B-Unaware trial showed no reduction of awareness or administration of volatile anaesthetic agent using BIS monitoring compared with monitoring end-tidal anaesthetic concentration (ETAC).[5] The BAG-RECALL trial demonstrated fewer episodes of awareness in an ETAC group compared with BIS, and the BIS-associated reduction of awareness had an NNT of 3333 with significant associated costs.[6]

Despite quality trials demonstrating conflicting results and a Cochrane review showing inconclusive evidence,[7] the use of DOA monitors is still recommended in patients undergoing relaxant GA or total intravenous anaesthesia (TIVA). Presumably, neuromuscular blocking drugs (NMBDs) conceal conscious behaviour. It is known that BIS levels in already anaesthetised patients decrease with reduced EMG activity associated with NMBD use, and this has been interpreted as EMG noise affecting BIS algorithms. Schuller and colleagues[1] demonstrated BIS values as low as 44 and 47 in fully conscious, paralysed patients, values that only returned to normal with the return of motor function. Despite the study limitation of low subject numbers, the consistent response may be evidence of a flaw in the algorithm of DOA monitors and places the validity of their use in the situation of relaxant anaesthesia in doubt.

The reliance on BIS technology may provide a false sense of security about the reduction in the risk of awareness, as stated by Avidan and colleagues[5] in the B-Unaware trial. Quality improvement measures being considered to address the lack of policies to prevent and manage awareness under anaesthesia are important,[8] but a measured approach to the continued use of DOA monitors, with their associated cost and conflicting reliability, is also important. Is it possible Schuller and colleagues' study establishes that we have not progressed further than the recommendation that avoidance or minimisation of paralysis is the most effective available method to prevent intraoperative awareness.[2]

Declaration of interest

None declared.

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Bis: looking beyond the number

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Editor—I note in the other comments about this exceptional paper[1] that the entire clinical picture should be considered. Given that TIVA in neuromuscularly blocked patients often involves the administration of remifentanil, one can expect there to be no concomitant clinical data to suggest awareness, due to the complete suppression of sympathetic nervous system responses to surgical stimulation that remifentanil produces. While subjective EEG waveform interpretation may increase the utility of BIS monitoring, I suspect that most working anaesthetists use the BIS number as their sole indicator of awareness/anaesthesia and modify the dose of the drugs accordingly.

Our profession has a long and inglorious history of failing in our principal pact with our patients, i.e. making them insensate. Over the years we have economised in our use of anaesthetic agents for various 'safety' reasons. We would do well to remember the spate of aware mothers undergoing caesarean section in the 1980s and 1990s as a result of our well-intentioned but unfounded worries about neonatal Apgar scores or concerns about bailing out of a difficult intubation.

Conflict of interest

I routinely use volatile anaesthesia, as I prefer to link anaesthetic delivery to life-supporting ventilation.

Reference

1. Schuller PJ, Newell S, Strickland PA, Barry JJ. Response of bispectral index to neuromuscular block in awake volunteers. *Br J Anaesth* 2015;**115**(Suppl 1):i95–103

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