Reduction in the incidence of awareness using BIS monitoring

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Background: Explicit recall (ER) is evident in approximately 0.2% of patients given general anaesthesia including muscle relaxants. This prospective study was performed to evaluate if cerebral monitoring using BIS to guide the conduction of anaesthesia could reduce this incidence significantly.

Patients and methods: A prospective cohort of 4945 consecutive surgical patients requiring muscle relaxants and/or intubation were monitored with BIS and subsequently interviewed for ER on three occasions. BIS values between 40 and 60 were recommended. The results from the BIS-monitored group of patients was compared with a historical group of 7826 similar cases in a previous study when no cerebral monitoring was used.

Results: Two patients in the BIS-monitored group, 0.04%, had ER as compared with 0.18% in the control group (P < 0.038). Both BIS-monitored patients with ER were aware during intubation when they had high BIS values (>60) for 4 min and more than 10 min, respectively. However, periods with high BIS = 4 min were also evident in other patients with no ER. Episodes with high BIS, 4 min or more, were found in 19% of the monitored patients during induction, and in 8% of cases during maintenance.

Conclusions: The use of BIS monitoring during general anaesthesia requiring endotracheal intubation and/or muscle relaxants was associated with a significantly reduced incidence of awareness as compared with a historical control population.

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greater than 60 during induction and maintenance. Adherence also to traditional indicators of level of consciousness was at the discretion of the individual anaesthesiologist.

The recorded BIS trends were stored in the non-volatile memory of an Aspect 2000 monitor until downloaded by the manufacturer’s representative in Sweden (Dansjö Medical AB, Stockholm, Sweden) at regular intervals. After all of the required number of patients had been enrolled, BIS trends were matched to the corresponding patient data by the investigators. No interim analyses were performed during the conduct of the study. The BIS trends were divided in three parts for analysis: induction, maintenance and emergence. The BIS data were analyzed for the induction and maintenance phases only, as values were expected to be > 60 during emergence. Rules were designed to allocate an eventual increase in BIS when an intravenous induction agent is redistributed from the CNS early after induction to the induction phase (see example in Fig. 1).

Definitions of BIS recordings (Fig. 1)

Induction phase
Rule 1-Start. In recordings showing a distinct ‘induction pattern’ (a stable period of BIS baseline threshold followed by a rapid decline of at least 10 units below baseline threshold), the start of the induction phase was defined as 90 s after that BIS has fallen 10 units below the baseline threshold.

Rule 2-Start. If a distinct ‘induction pattern’ did not exist as described above, the start of the induction phase was defined as the first observation in the BIS trend. The end of the induction phase was 10 min after what was considered as start according to Rules 1 or 2.

Maintenance phase
The maintenance phase started immediately after the induction phase.

Rule 1-End. In recordings where a distinct BIS level immediately prior to induction is identified, the maintenance phase is considered to end 15 min before that BIS returned to 10 units below the baseline threshold provided that the recording is ended in 3 min thereafter or no further BIS values less than 75 are recorded.

Rule 2-End. If BIS > 60 was evident during the last 5 min of the maintenance phase (Rule 1-End) and the manual anaesthesia record indicated that surgery was already completed, the recorded time for end of surgery was chosen as end of the maintenance phase.

Rule 3-End. If the trend did not show an ending as described in Rule 1-End, the end of the maintenance phase is defined as 15 min before the last recorded data in the BIS trend.

Rule 4. In very short cases, no maintenance phase was evident according to definitions of induction and emergence phases. In those cases the manually recorded times for start and end of surgery were chosen for defining the maintenance phase.

The definitions were applied by a computerized program and all trends were subsequently checked by inspection by two of the authors (MLL and RS).

Assessments of BIS use by anaesthesiologists
The anaesthesiologists assessed to what extent BIS had been used for guiding anaesthesia on a 100-mm visual analogue scale (VA-scale ranging from 0 = none to 100 = completely), and also, on a separate VA-scale, they assessed to what extent they felt confident that the BIS monitor had worked properly.

Patient interviews
The patients were interviewed for awareness on three occasions, using the modified Brice interview (3), before they left the post anaesthesia care unit, and 1–3 days and 7–14 days after the operation. Patients who responded that they did remember something in-between falling asleep and waking up were interviewed in depth. The incidence of awareness observed in patients with BIS monitoring were compared with similar data (patients receiving muscle relaxants or endotracheal intubation) from the previously reported study in the same two institutions at a time when neurophysiological monitoring was
The primary outcome measure was incidence of awareness at any time during surgery.

**Statistics**

Analyses were performed on an intention-to-treat basis based on whether BIS had been used or not. Analysis of the outcome of awareness was performed using Fisher’s exact test. For demographic and procedural data the Student’s *t*-test, double-sided, or the Chi-square test with Yate’s correction were used as appropriate. A *P*-level of 0.05 was accepted as significant.

**Results**

The inclusion period was continued for 17 months. Awareness outcome data was collected from 5057 patients. Forty-six cases were excluded from trend analysis because the corresponding BIS trend was unavailable, and a further 66 patients were excluded due to poor quality or discontinuous trends or failure to conduct any of the two last interviews for awareness. No cases of awareness were reported among the 112 excluded cases. Thus, 4945 patients remained for the final analysis. A comparison of the BIS monitored and control populations is presented in Table 1. Start of the induction phase was identified according to Rule 1-Start in 4901 (99%) of the patients although, eventually, Rule 4 was used in 56 of these cases. Rule 2-Start was used in the remaining 44 cases. The end of the maintenance phase was defined according to Rule 1-End in 4092 (92%) patients, Rule 2-End was applied in 385 patients, Rule 3-End in 412 cases and Rule 4 in 56 cases.

The number of awareness cases in the BIS-monitored group (n = 2) was statistically significantly fewer compared with the historical control group (n = 14) as determined by Fisher’s exact test, *P* = 0.019 (single sided) and *P* = 0.038 (double sided) (Fig. 2). This corresponds to a 77% reduction in the incidence of awareness in the BIS-monitored group. The average BIS during the induction phase was 46 ± 11. BIS < 40 was evident for 4 ± 4 min, and BIS > 60 for 2 ± 3 min during induction (Fig. 3). In this phase, episodes with BIS > 60 for 4 min or more were evident in 962 cases (19%), and BIS > 70 for 4 min or more in 198 patients (4%). During the maintenance phase the average BIS was 38 ± 8 (Fig. 4), and BIS > 60 was evident for 2 ± 9 (0–172) min (Fig. 5). In 414 patients (8%), a total of 669 episodes of BIS > 60 for at least 4 min were identified during maintenance. If BIS > 70 is considered during maintenance, this was evident for 0.5 ± 4.5 (0–142) min. A total of 143 episodes of BIS > 70 for at least 4 min were identified during maintenance. The VA-scale rating concerning to what extent BIS had guided the conduction of anaesthesia was 41 ± 32. The corresponding rating concerning reliability was 79 ± 20. The most frequently cited concern regarding reliability was interference due to electrocautery reported in 21% of cases.

Table 1

Comparison of treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>No BIS</th>
<th>BIS monitored</th>
<th><em>P</em>-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>7826</td>
<td>4945</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 19</td>
<td>50 ± 19</td>
<td>0.0038</td>
</tr>
<tr>
<td>ASA physical status</td>
<td>1.5 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>114 ± 72</td>
<td>121 ± 72</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 9</td>
<td>170 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 15</td>
<td>75 ± 16</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female/Male (%)</td>
<td>64/36</td>
<td>61/39</td>
<td>0.0013</td>
</tr>
<tr>
<td>Acute surgery (%)</td>
<td>25</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Time to last interview (days)</td>
<td>11 ± 2</td>
<td>9 ± 3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Premedication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1818(23%)</td>
<td>967(20%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>No premedication</td>
<td>2113(27%)</td>
<td>2306(47%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid before induction</td>
<td>7550(96%)</td>
<td>4383(89%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Induction agent</td>
<td>33/66</td>
<td>28/71</td>
<td>0.0001</td>
</tr>
<tr>
<td>(Propofol/Thiopental) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total intravenous anaesth. (%)</td>
<td>3.7</td>
<td>5.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Concomitant regional anaesth.</td>
<td>752(10%)</td>
<td>664(13%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>7752(99%)</td>
<td>4729(96%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intubated</td>
<td>7796(100%)</td>
<td>4926(100%)</td>
<td>NS</td>
</tr>
<tr>
<td>End tidal gas monitoring</td>
<td>6028(80%)</td>
<td>4688(99%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

(% of inhalation anaesthesia)
Descriptions of awareness cases

Case 1 (Fig. 6A)
This patient was a 17-year-old, healthy, non-smoking female, height 165 cm, weight 65 kg, ASA physical status 1, scheduled for elective day case dental surgery (extraction of retained molars). This case occurred at the very beginning of the inclusion period of the study. She had had general anaesthesia without complications several times before. The patient received 1 g of acetaminophen and 50 mg of diclofenac orally 45 min before induction. No other premedication was given. Induction was with 250 mg of thiopental sodium, 0.1 mg of fentanyl and 40 mg of rocuronium. Nasal intubation was difficult and prolonged. After intubation, maintenance was with sevoflurane in nitrous oxide/oxygen. Anaesthesia lasted for 115 min. The patient reported awareness at all three interviews and at a follow-up interview 5 weeks after surgery. Her description was consistent on all occasions. She described that she had felt her neck was bent and that something was placed in her left nostril. Although it was actually not very painful she wanted to say that it did hurt, but was she not able to. She tried to open her eyes and move but could not. She immediately understood the situation. She could not tell how long wakefulness had lasted and the memories were somewhat ‘patchy’. She had no visual or auditory memories. At the last two interviews she was offered to discuss this event with a ‘professional person’, specialized in the area, but she did not feel any need for that.

Case 2 (Fig. 6B)
Male, 22 years old, height 186 cm, weight 87 kg, healthy non-smoker and ASA 1. Spontaneous right-sided pneumothorax, scheduled for thoracoscopy and pleurectomy because of failed drainage treatment. No premedication was given. Induction was with 400 mg of sodium thiopental, 0.25 mg of fentanyl and 50 mg of rocuronium. Uncomplicated intubation with a double-lumen tube was performed by an anaesthesiologist.
under training. Maintenance of anaesthesia was with sevoflurane in air/oxygen. Anaesthesia lasted 100 min. The patient reported awareness at all three interviews and at a follow-up interview 6 weeks after surgery. He described feeling the tube halfway down his throat and at the same time seeing the operating theatre for fractions of a second and then he faded away. He felt no pain and did not hear anything. He did not try to move. He understood the situation when he woke up in the post anaesthesia care unit. He also remembered dreaming during surgery but he could not retrieve its contents. At the follow-up interview he was offered to discuss this event with a ‘professional person’, specialized in the area, but he did not feel any need for that.

Discussion
In this study two patients with explicit recall corresponding to a 0.04% incidence rate were identified when BIS monitoring was used to guide general anaesthesia. This is significantly less than the 0.18% incidence obtained in a well-matched group of patients in a previous study conducted 4 years earlier at the same two institutions (1). The present incidence of awareness is the lowest ever reported in a reasonably large study using muscle relaxants.

It is important to note that high BIS values >60 were present at the time of awareness during tracheal intubation in both BIS-monitored patients. This suggests that if this information, about the need for additional anaesthetics, had been used to guide the administration, no cases of awareness would have been identified. This is strengthened by the fact that it was acknowledged that no attention was paid to the BIS monitor during intubation in either of these cases. However, BIS values >60 were evident in some other patients with no ER. It has previously been reported that the likelihood for awareness increases with time at higher BIS values (4). In Case 1, BIS > 60 was evident for at least 10 min. In Case 2 (Fig. 6B), the fall in BIS value after induction was interrupted after 1 min and BIS > 60 was thereafter evident for approximately 4 min. When we studied the induction trends from all of the patients who did not report ER, we found BIS > 60 for 4 min or more in 19%, and BIS > 70 in 4% of cases. Trends like that in Case 2 (Fig. 6B), showing a peak in BIS when the effect of an intravenous induction bolus wears off due to redistribution, which also often coincide with laryngoscopy and intubation, were observed fairly often in this study. Episodes of high BIS without ER were found also during maintenance. In the maintenance phase 8% of patients had at least one episode of BIS > 60 for 4 min or more, and 1.7% of patients had BIS > 70 for 4 min or more. Even if some of the high BIS values we identified were due to problems with signal quality or artifact, it seems that ER is evident in only a fraction of patients showing BIS values >60 for 4 min or more. This may be due to amnesia (4), but also to interindividual variability in the relation between cognitive capacity and BIS (5). Taken together, our results may indicate that while the specificity of high BIS is less than 100% for identifying subsequent ER, the sensitivity while using an upper limit of 60 is satisfactory for avoiding ER. In addition to the present result concerning the reduction in the incidence of ER with cerebral monitoring, the apparent increased risk for awareness during intubation is again illustrated (1) both by the two awareness cases and by the BIS ‘rebound’ found in several patients when the induction agent is redistributed from the CNS.

It is important to consider the context of how our findings were obtained. In our earlier study, we
reported that the use of traditional forms of monitoring, including end-tidal inhalational agent concentration analysis, did not appear to be effective in preventing awareness and speculated on the potential use of newer neuromonitors. Rather than attempting to conduct a prospective, randomized trial, we sought to conduct a more natural study illustrating the results that can be expected when BIS is incorporated into a department-wide routine monitoring practice. That is, when all members of the anaesthesia team use this technology, not only particularly interested anaesthesiologists in selected cases. On average, anaesthesia was rather deep (BIS 38±8) during maintenance as related to the recommended BIS interval (40—60). The prevalence of both low (<40) and high (>60) BIS values in our study may indicate that prior experience and opinions how to conduct anaesthesia including adherence to haemodynamic variables still had a substantial impact on the drug administration. This is also illustrated by the fact that the anaesthesia providers subjectively rated the extent to which BIS had been used to guide anaesthesia to about 40% (41 ± 32 on a 100-mm VA-scale). The extent to which BIS was considered to work properly and give reliable readings was assessed as 79 ± 20 on a 100-mm VA-scale. Electrocautery, the most prevalent cause of interference, was reported to have influenced the BIS monitoring at some point in the case in 21% of monitored patients while no significant disturbance was recognized in 57% of cases. As previously stated, better adherence to the BIS monitoring may have given an even more favourable result in terms of ER, but we assume that the present result represents a conservative estimate of what to expect from this monitoring when recently introduced in clinical routine.

Distinguishing between true ER and other memories is not always straightforward. In the present study 20 patients responded to the Brice interview that they did ‘remember something in between’ and were therefore interviewed in depth. Only the two described cases described experiences suggestive for ER. In our prior study, we encountered a similar number of unsubstantiated initial reports.

Due to the non-randomized study design, it is possible that other changes in clinical practice or knowledge that the study of the BIS monitor was being conducted may have been responsible for our findings.

The large numbers of patients included in this study were necessary for assessing the primary outcome, ER. However, this very large sample size allows minor clinically non-significant differences between treatment groups to be identified as statistically significant. The only difference between the groups in Table 1 that we regard as clinically significant for potentially offering an alternative explanation for the present result is the increased fraction of patients with end-tidal gas monitoring in the BIS-monitored group. Thus, it is possible that the increased availability of end-tidal gas monitoring in the BIS-monitored patients as compared with the historical control cohort has contributed to the present result, although we found no evidence for this assumption in a previous study (1). On the other hand, fewer patients in the BIS-monitored cohort received premedication or opioids before induction, so it could be argued that this treatment group was exposed to a higher risk of experiencing awareness, especially during induction.

Despite the theoretical limitations of our non-randomized study design, it is interesting to note that our finding of a 77% reduction in awareness incidence in our general, non-cardiac population is in close agreement with the 82% reduction of awareness in high-risk patients enrolled in a prospective, randomized study reported in an abstract by Myles (6).

**Conclusion**

The use of BIS monitoring during general anaesthesia requiring endotracheal intubation and/or muscle relaxants was associated with a significantly reduced incidence of awareness as compared with a historical control population.

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