Clinical effectiveness and cost-effectiveness of depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend): a systematic review and economic evaluation

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Scientific summary

Effectiveness of depth of anaesthesia monitoring

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Scientific summary

Background

It is important that the level of general anaesthesia (GA) is appropriate for the individual patient undergoing surgery. If anaesthesia is deeper than required to keep a patient unconscious, there might be increased risk of anaesthetic-related morbidity, such as postoperative nausea, vomiting and cognitive dysfunction. If anaesthesia is too light, patients may not be fully unconscious and could be at risk of intraoperative awareness. Intraoperative awareness is a relatively rare event with an incidence typically of around one to two patients per 1000. However, over time, awareness may cause depression, anxiety and post-traumatic stress disorder (PTSD).

During GA, patients are routinely monitored for signs of potential intraoperative awareness, including tachycardia (rapid heart rate), hypertension, sweating, lacrimation (tear production), movement/grimacing and tachypnoea (rapid breathing). In patients receiving inhaled GA, end-tidal (exhaled) anaesthetic gas concentrations may be assessed to gauge depth of anaesthesia. However, clinical observation alone may not be a reliable surrogate marker of depth of anaesthesia. Technologies have been developed using electroencephalography (EEG) to measure and interpret electrical activity in the brain to provide a measure of unconsciousness. Most devices comprise a module that collects raw EEG data via sensors placed on the patient’s forehead and then processes and analyses these using a mathematical algorithm. The output is then displayed numerically on a monitor for use by the anaesthetist to judge depth of unconsciousness, and to alter anaesthetic dose accordingly. Three such devices prioritised for this report are Bispectral Index (BIS), E-Entropy and Narcotrend.

Objectives

The objective of this report is to assess the clinical effectiveness and cost-effectiveness of BIS, E-Entropy and Narcotrend technologies to monitor the depth of anaesthesia in surgical patients undergoing GA.

Methods

Systematic review of patient outcomes

A systematic review of patient outcomes associated with depth of anaesthesia monitoring was conducted. A search strategy was developed and run on eight bibliographic electronic databases. Reference lists supplied by the device manufacturers were checked to identify potentially relevant studies. Eligibility criteria were applied to titles and abstracts and to full papers by two reviewers independently. Because of the relatively large volume of evidence for BIS, we included only trials that were supplemental to a recent Cochrane systematic review of BIS. Included studies were data extracted using a standard template. Risk of bias and markers of quality were assessed. The studies were synthesised narratively, with meta-analyses from the Cochrane review of BIS updated with supplemental studies where feasible and appropriate.

Systematic review of cost-effectiveness

A systematic review of the literature on the cost-effectiveness of depth of anaesthesia monitoring compared with standard clinical monitoring was undertaken. Included studies were evaluated for their quality and for generalisability to the UK. Eligibility criteria were applied to titles and abstracts and to full papers by two reviewers independently, and the studies were synthesised narratively.
Economic evaluation

A decision-analytic model was developed to assess the cost-effectiveness of depth of anaesthesia monitoring compared with standard clinical observation. A simple decision tree was developed, which accounted for patients’ risk of experiencing short-term anaesthetic-related complications in addition to a risk of experiencing intraoperative awareness.

It was assumed that a proportion of patients who experience awareness will suffer psychological symptoms and that a proportion of those will develop PTSD and may seek treatment. A systematic review of health-related quality of life (HRQoL) in PTSD was undertaken in order to estimate the quality-of-life decrement to be applied as the result of any psychological symptoms arising from an awareness episode. The costs of depth of anaesthesia monitoring consist of the capital costs associated with acquisition of the monitor and recurring costs associated with sensors that are attached to the patient. Equivalent annual costs for each monitor were calculated for an effective equipment life of 5 years. Unit costs of anaesthetic drugs were derived from the British National Formulary (BNF) and supplied from an NHS Trust. The baseline incidence of awareness in high-risk patients was calculated from the control arms of randomised controlled trials (RCTs) in this group of patients. The summary values of the effectiveness of depth of anaesthesia monitoring were taken from our systematic review of patient outcomes.

The model evaluates costs [UK sterling (pounds) using a 2011 price base] from the perspective of the NHS and Personal Social Services. Outcomes in the model are expressed as quality-adjusted life-years (QALYs). Both costs and outcomes are discounted using a 3.5% annual discount rate, in line with current guidance.

Results

Systematic review of patient outcomes

From a total of 776 bibliographic records, 22 RCTs comparing BIS, E-Entropy and Narcotrend with standard clinical monitoring were included in the systematic review of patient outcomes. Fifteen trials of BIS, seven trials of E-Entropy and four trials of Narcotrend all compared with standard clinical monitoring. (Note that some trials compared more than one of the three devices to standard clinical monitoring.) Some of the trials reported that in the EEG arm anaesthesia doses were titrated according to device values in conjunction with clinical signs. In other trials the use of clinical signs alongside EEG monitoring was not explicit. The Cochrane review of BIS included 31 RCTs. The trials included in both reviews span the period between 1997 and 2011 in terms of publication date.

In many cases, the risk of bias in the trials was unclear because of limitations in reporting of methodological details. The trials varied in terms of their sample sizes, from as low as 20 to over 6000 patients, but, in general, sample sizes were relatively small (e.g. fewer than 200). Fifteen of the trials in this systematic review and all of the trials in the Cochrane BIS review were conducted in adult patients, of varying mean ages. Seven of the trials in this review were conducted with children. The trials were generally single-centre studies conducted in a range of locations including Europe, North America and Asia.

Six trials were conducted with patients classified as having one or more risk factors for intraoperative awareness (e.g. planned cardiac surgery, pulmonary hypertension, end-stage lung disease), all of which evaluated BIS monitoring. The trials tended to exclude patients with significant ill health or factors that may interfere with EEG recordings.

Explicit intraoperative awareness was assessed in 16 of the trials, but in most of these no episodes were recorded. However, awareness is a relatively rare event and the trials were not statistically powered to detect it. The six trials of patients classified with risk factors for intraoperative awareness, all of which evaluated BIS, were combined in a fixed-effect meta-analysis. The overall pooled Peto’s odds ratio (OR) was 0.45 [95% confidence interval (CI) 0.25 to 0.81] in favour of BIS.
Caution is advised in the interpretation of this result as, overall, there was statistically significant heterogeneity \( (p = 0.009; I^2 = 79\%) \). Both the subgroup of trials, which included a trial of mixed inhaled and intravenous anaesthesia, and the subgroup, which included trials of total intravenous anaesthesia (TIVA), statistically favoured BIS monitoring. However, in the subgroup of trials that used only inhaled anaesthesia, the Peto’s OR was 1.79 (95% CI 0.63 to 5.11), favouring standard clinical monitoring, although not statistically significant.

**Systematic review of cost-effectiveness**

A total of 134 potentially relevant references were identified by the cost-effectiveness searches. Of these, one study comparing BIS with standard clinical monitoring met all of the inclusion criteria. The study reported cost per avoided intraoperative recall, with the incidence of recall with BIS reported as 0.04% compared with 0.18% for standard monitoring, resulting in a cost per avoided recall of US$4410. The authors of the study concluded that BIS monitoring did not appear cost-effective. However, the results and conclusions should be viewed with caution because of poor methodological and reporting quality.

**Economic evaluation**

For each technology we presented a base-case analysis for two modes of anaesthetic administration {TIVA and mixed anaesthesia [induction with intravenous (i.v.) anaesthesia and maintenance with inhaled anaesthesia or a combination of inhaled and i.v. anaesthetic]} and for two patient populations (those considered at high risk of intraoperative awareness and a general surgical population, at average risk of intraoperative awareness).

**Bispectral Index compared with standard clinical monitoring**

In cohorts of 10,000 patients at high risk of intraoperative awareness undergoing GA with TIVA, the incremental cost-effectiveness ratio (ICER) for BIS compared with standard clinical monitoring in this population was £22,339.

For the population of general surgical patients undergoing GA with TIVA, BIS monitoring was modelled as being associated with 3.8 cases (per 10,000 patients) of awareness, compared with 16 in patients receiving standard clinical monitoring. Given the lower baseline risk of awareness in this population, the QALY gain with BIS monitoring was lower (0.0003) than for high-risk patients. This resulted in a higher ICER (£34,565).

Deterministic sensitivity analyses indicated that the ICER was sensitive to the same input parameters as for the population at high risk of awareness.

The baseline estimates of awareness, late psychological symptoms (LPS) and PTSD for high-risk patients undergoing mixed GA were the same as for high-risk patients undergoing TIVA. However, given that the OR of awareness with BIS monitoring was higher in this analysis, the estimated reduction in LPS and PTSD was lower. The ICER for BIS compared with standard clinical monitoring in this population was £29,634.

The baseline estimates of awareness, LPS and PTSD in the population of general surgical patients undergoing mixed GA were the same as for TIVA. Although a proportion of the higher cost associated with BIS monitoring was offset by reduction in anaesthetic consumption, the cost-saving for inhaled anaesthesia was lower than for TIVA. As a result the incremental cost was greater. Given the lower baseline risk of awareness in this population, the QALY gain with BIS monitoring was lower (0.0003) than for high-risk patients, resulting in a higher ICER (£49,198).

Deterministic sensitivity analyses indicated that the ICER was sensitive to a number of parameters, including the baseline incidence of awareness and the effectiveness of BIS in reducing awareness.
**E-Entropy compared with standard clinical monitoring**

In patients at high risk of awareness undergoing GA with TIVA, the modelled cost per patient with E-Entropy monitoring was higher than with standard clinical monitoring, although some of the additional cost was offset by reduced cost associated with psychological sequelae of awareness. The ICER for E-Entropy compared with standard clinical monitoring in this population was £14,421.

In the population of general surgical patients undergoing GA with TIVA, E-Entropy monitoring had a higher cost per patient than standard clinical monitoring. There was no reduction in anaesthetic drug costs to offset the additional costs of E-Entropy monitoring. Given the lower baseline risk of awareness in this population, the QALY gain was lower than for high-risk patients, which resulted in a higher ICER (£31,131–31,430).

In patients considered at high risk of awareness undergoing mixed GA, E-Entropy monitoring had higher costs and improved outcomes compared with standard clinical monitoring. However, the QALY gain was lower than for patients undergoing TIVA. The ICER for E-Entropy compared with standard clinical monitoring in this population was £19,367.

In the population of general surgical patients undergoing mixed GA, E-Entropy monitoring had higher costs than standard clinical monitoring. In contrast with the analysis for TIVA, the clinical trial used to estimate inhaled anaesthetic drug consumption reported a substantial decrease (29%), which resulted in approximately half of the additional cost of E-Entropy monitoring being offset by a reduction in anaesthetic drug costs. Despite the lower baseline risk of awareness, which resulted in a lower QALY gain with E-Entropy monitoring than for high-risk patients, the lower incremental cost resulted in an equivalent ICER (£19,000).

Deterministic sensitivity analyses indicated that the ICER was sensitive to a number of parameters, including the baseline incidence of awareness and the effectiveness of E-Entropy in reducing awareness.

**Narcotrend compared with standard clinical monitoring**

In patients at high risk of awareness undergoing GA with TIVA, the modelled cost per patient with Narcotrend monitoring was higher than with standard clinical monitoring, although some of the additional cost was offset by reduced cost associated with psychological sequelae of awareness. The ICER for Narcotrend compared with standard clinical monitoring in this population was £5681. Deterministic sensitivity analyses indicated that the ICER was sensitive to a number of parameters, including the baseline incidence of awareness and the effectiveness in reducing awareness.

In the general surgical population undergoing GA with TIVA, and also undergoing mixed GA, Narcotrend monitoring had a lower cost per patient than standard clinical monitoring. The additional cost of monitoring was more than offset by reduction in anaesthetic drug consumption. Given the lower baseline risk of awareness in this population, the QALY gain was lower than for high-risk patients. Narcotrend dominated standard clinical monitoring. Narcotrend remained dominant in the majority of deterministic sensitivity analyses.

In patients at high risk of awareness undergoing mixed GA, Narcotrend monitoring had higher costs and improved outcomes than standard clinical monitoring, although the QALY gain (0.0005) was lower than for patients undergoing TIVA. The ICER for Narcotrend compared with standard clinical monitoring in this population was £8033. Deterministic sensitivity analyses indicated that the ICER was sensitive to the same parameters as for high-risk patients undergoing TIVA.
Conclusions

In general, BIS, E-Entropy and Narcotrend technologies for monitoring the depth of anaesthesia are associated with reductions in general anaesthetic consumption, and decreased anaesthetic recovery times, compared with monitoring of clinical signs alone. However, these reductions may be considered clinically modest. The available evidence on the impact of the technologies on reducing the likelihood of intraoperative awareness is limited. Overall, BIS was associated with a statistically significant reduction in intraoperative awareness in patients classified as at higher risk, although there is uncertainty in effect estimates because of significant heterogeneity. Caution is advised because of uncertainties about the risk of bias of many of the included trials, and because many outcome measures were not statistically powered.

The cost-effectiveness of depth of anaesthesia monitoring appears to be highly dependent on the incidence of awareness, the HRQoL impact of psychological sequelae of awareness and the probability of developing psychological illness following awareness, as well as the effectiveness of depth of anaesthesia monitoring in reducing awareness. Cost-savings resulting from reduced use of anaesthetic drugs may offset some of the additional cost of depth of anaesthesia monitoring. The cost of sensors attached to the patient appears to be a key factor in the additional cost of depth of anaesthesia monitoring.

This report makes the following research recommendations (in priority order):

1. RCTs of E-Entropy- and Narcotrend-guided anaesthesia monitoring are needed, in high-risk patients, with adequate statistical power to detect explicit intraoperative awareness, and of sufficient length of follow-up to detect delayed cases of awareness.
2. RCTs of all three technologies should also evaluate the effects of anaesthesia overdosing, including short-term effects, such as nausea and vomiting, as well as longer-term impact on cognitive function.
3. RCTs of E-Entropy- and Narcotrend-guided anaesthesia monitoring are also needed in children.

Study registration

This study is registered as PROSPERO CR042011001834.

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Publication

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This report

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