Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial

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Summary

Background Awareness is an uncommon complication of anaesthesia, affecting 0·1–0·2% of all surgical patients. Bispectral index (BIS) monitoring measures the depth of anaesthesia and facilitates anaesthetic titration. In this trial we determined whether BIS-guided anaesthesia reduced the incidence of awareness during surgery in adults.

Methods We did a prospective, randomised, double-blind, multicentre trial. Adult patients at high risk of awareness were randomly allocated to BIS-guided anaesthesia or routine care. Patients were assessed by a blinded observer for awareness at 2–6 h, 24–36 h, and 30 days after surgery. An independent committee, blinded to group identity, assessed every report of awareness. The primary outcome measure was confirmed awareness under anaesthesia at any time.

Findings Of 2463 eligible and consenting patients, 1225 were assigned to the BIS group and 1238 to the routine care group. There were two reports of awareness in the BIS-guided group and 11 reports in the routine care group (p=0·022). BIS-guided anaesthesia reduced the risk of awareness by 82% (95% CI 17–98%).

Interpretation BIS-guided anaesthesia reduces the risk of awareness in at-risk adult surgical patients undergoing relaxant general anaesthesia. With a cost of routine BIS monitoring at US$16 per use in Australia and a number needed to treat of 138, the cost of preventing one case of awareness in high-risk patients is about $2200.

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Introduction

Anaesthesia can be defined as a state of drug-induced unconsciousness in which the patient neither perceives nor recalls noxious stimulation.[1] Awareness is the postoperative recollection of events occurring during general anaesthesia. The incidence of awareness is 0·1–0·2% in the general surgical population,[2,3] but is greater during cardiac surgery, caesarean section, and trauma surgery.[4-6]

Awareness is a distressing complication of anaesthesia.[7–10] Affected patients report perception of paralysis, conversations, and surgical manipulations, accompanied by feelings of helplessness, fear, and pain. Some patients have rated it as their worst hospital experience;[6] post-traumatic stress disorder can develop in those who are severely affected.[8-10] However, despite numerous attempts over more than 150 years, the definitive monitor for predicting awareness has not been established.[11]

Clinical signs, such as blood pressure and heart rate, are routinely used by anaesthetists to monitor anaesthetic depth, but such methods are unreliable.[5] Early attempts to monitor anaesthetic depth using the spontaneous[11-14] or evoked[15,16] electroencephalograph were also unsuccessful. The bispectral index (BIS) is a monitor of anaesthetic depth approved by the Food and Drug Administration in the USA. BIS incorporates time-domain, frequency-domain, and bispectral analysis of the electroencephalograph, and is displayed as a dimensionless number between 0 (deep anaesthesia) and 100 (awake),[17] with 40–60 being suitable for surgical anaesthesia.[18] BIS correlates well with hypnotic state and anaesthetic drug concentration,[19-21] and use of BIS can shorten recovery times.[18,22] However, the predictive value of BIS as a monitor for awareness has not previously been assessed in a randomised trial.[11,23,24] We therefore did a large trial to assess whether BIS monitoring decreases the incidence of awareness during relaxant general anaesthesia in routine surgical patients at high risk of awareness.

Methods

Study population

Surgical patients undergoing relaxant general anaesthesia at one of the participating centres (listed at the end of the paper) were eligible if they were aged 18 years or older, and had at least one of these risk factors for awareness: caesarean section, high-risk cardiac surgery (eg, ejection fraction <30%, cardiac index <2·1 L/min per m^2, severe aortic stenosis, pulmonary hypertension, or undergoing off-pump coronary artery bypass graft surgery), acute trauma with hypovolaemia, rigid bronchoscopy, significant impairment of cardiovascular status and expected intraoperative hypotension requiring treatment, severe end-stage lung disease, past history of awareness, anticipated difficult intubation where an awake intubation

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technique was not planned, known or suspected heavy alcohol intake, chronic benzodiazepine or opioid use, or current protease inhibitor therapy. Patients were excluded if they had inadequate comprehension of the English language, traumatic brain injury, memory impairment, psychosis, known or suspected electroencephalograph abnormality (eg, epilepsy, previous brain resection, or scarring), or were not expected to be available for interview postoperatively.

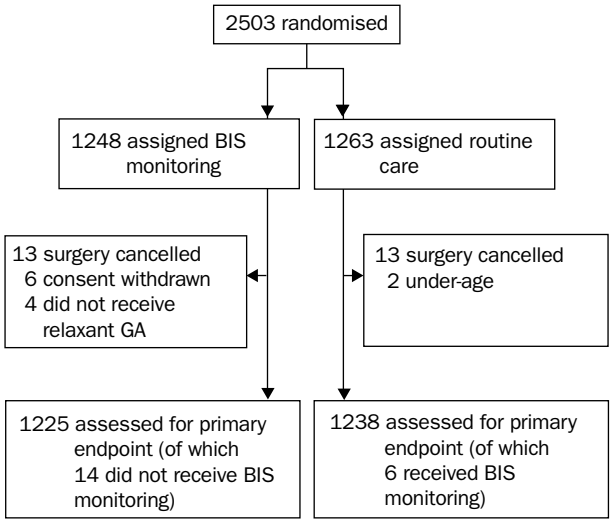
The protocol was approved by the ethics committee of each participating centre. All elective surgical patients gave written informed consent before enrolment. Conscious emergency surgery patients were given a brief verbal description of the trial. Their next-of-kin was given a comprehensive written information statement and was asked to sign an acknowledgment form approved by the ethics committee. All such patients who survived were approached in the postoperative period and written consent was obtained. Patients were enrolled between September, 2000, and December, 2002.

Procedures

The trial was a multicentre, double-blind, randomised parallel group study. Patients were randomly assigned to receive BIS-guided anaesthesia (BIS group) or routine anaesthesia care (routine care group). All other aspects of perioperative care were unaffected. After consent was obtained and immediately before induction of anaesthesia the anaesthetist rang the co-ordinating centre to obtain a computer-generated random group allocation. Follow-up was undertaken by a blinded observer, with a structured interview, and an independent endpoint adjudication committee was established.

All patients received usual preoperative care, including routine anaesthetic and safety monitoring. Choice of anaesthetic agents, muscle relaxants, and perioperative analgesia was left to the anaesthetist. Combined general-regional anaesthetic techniques were permitted. A BIS sensor was applied to every patient's forehead before induction of anaesthesia and connected to an A-2000 BIS monitor (version 3.4, default settings; Aspect Medical Systems, Newton, MA, USA) that was concealed from the patient. In patients allocated to the routine care group, the monitor was not turned on. In patients allocated to the BIS group, BIS monitoring commenced and the delivery of anaesthesia was adjusted to maintain a BIS of 40–60 from the start of laryngoscopy to the time of wound closure. The BIS number and trend were displayed for the anaesthetist; alarm limits were not specified and in most cases were left off (default position). Hypnotic drug titration to a BIS of 55–70 was allowed during wound closure, in order to facilitate early recovery.[18] Anaesthetic drugs were administered by the anaesthetist according to their clinical judgment. Anaesthetists were informed that for all patients in both groups, if clinically appropriate, reduction and cessation of general anaesthesia should be timed to allow early recovery after final wound closure and application of dressings.

The study protocol stipulated that anaesthetists manually record the BIS value at 5-min intervals for the first hour, and every 10 min thereafter, for each patient allocated to the BIS group. The time-averaged mean BIS value was calculated. The highest and lowest BIS readings that persisted for at least 5 min were recorded.



Trial profile
GA=general anaesthesia. BIS=bispectral index.

	BIS group (n=1225)	Routine care group (n=1238)
Age (years)*	58·1 (16·5)	57·5 (16·9)
Male sex	752 (61)	784 (63)
Weight (kg)*	72·7 (17·6)	74·2 (17·7)
ASA status		
1	111 (9%)	127 (10%)
2	179 (15%)	227 (18%)
3	542 (44%)	520 (42%)
4	388 (32%)	354 (29%)
5	5 (0·4%)	10 (0·8%)
Emergency surgery	180 (15%)	175 (14%)
Risk group†		
High-risk cardiac surgery	362 (30%)	373 (30%)
Off-pump cardiac surgery	185 (15%)	189 (15%)
Impaired cardiovascular status	305 (25%)	306 (25%)
Acute trauma with hypovolaemia	28 (2·3%)	34 (2·8%)
Caesarean section under general anaesthesia	80 (6·5%)	92 (7·4%)
Bronchoscopy, laryngoscopy, or both	127 (10·4%)	117 (9·5%)
History of awareness	85 (6·9%)	98 (7·9%)
Anticipated difficult intubation	52 (4·2%)	37 (3·0%)
Heavy alcohol intake	70 (5·7%)	106 (8·6%)
Chronic use of benzodiazepine, opioids, or both	129 (10·5%)	129 (10·4%)
Protease inhibitor therapy	6 (0·5%)	6 (0·5%)
Severe end-stage lung disease	60 (4·9%)	43 (3·5%)
Extent of surgery		
Minor	104 (9%)	104 (8%)
Intermediate	216 (18%)	231 (19%)
Major	905 (74%)	903 (73%)
Pre-existing medical conditions†		
Respiratory	307 (25%)	281 (23%)
Cardiovascular	779 (64%)	771 (62%)
Endocrine	223 (18%)	232 (19%)
Other	267 (22%)	240 (19%)
Preoperative HAD scale‡§		
Anxiety score	6 (3–10)	6 (3–9)
Depression score	4 (2–7)	3 (2–6)
Sedative premedication	674 (55%)	711 (57%)
Duration of anaesthesia (h)§		
All patients	3·2 (1·5–4·4)	3·1 (1·3–4·5)
Excluding ICU patients (n=1123)	1·3 (0·7–2·5)	1·3 (0·7–2·5)

Data are number (%) unless otherwise stated. ASA=American Society of Anesthesiologist's physical status score. ICU=intensive care unit. *Data are mean (SD). †Some patients were in more than one risk group category. ‡HAD= Hospital anxiety and depression scale (range 0 [lowest level] to 21); data were obtained for 1033 patients in the BIS group and 1011 in the routine care group—these data were not obtained for emergency patients. §Data are median (IQR).

Table 1: **Characteristics of patients at entry**

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We also recorded the amount of time that BIS was greater than 60 up until the time of wound closure, as a possible indicator of insufficient anaesthesia.

The primary outcome measure was the incidence of confirmed awareness, which was defined by the patient's recollection of intraoperative events, by use of a structured questionnaire.[3] Interviews were scheduled on three occasions after surgery because postoperative recollections can be transient.[3,25] The first interview was done after the patient had recovered from general anaesthesia (2–6 h after surgery). Subsequent interviews were done at 24–36 h and 30 days postoperatively. All potential awareness episodes were followed up, with the anaesthetist providing a narrative report that did not include group identity to an independent endpoint adjudication committee of three experienced anaesthetists. Each member of the committee independently coded each report as "awareness", "possible awareness", or "no awareness". Confirmed awareness was defined as a unanimous coding of "awareness" or two members coding as "awareness" and the third as "possible awareness". "Possible awareness" was defined as one or more coding of the report as "awareness" or "possible awareness".

Secondary outcome measures were possible awareness, recovery times, hypnotic drug administration, incidence of marked hypotension (defined as systolic blood pressure less than 90 mm Hg and needing vasoactive drug treatment), anxiety and depression measured by a validated scale,[26] patient's satisfaction on a five-point scale, major complications, and 30-day mortality. Recovery times were measured from completion of wound dressing and for most patients included eye opening and eligibility for discharge from the post-anaesthesia care unit, defined as an Aldrete score[27] of 9 or greater. For patients who were mechanically ventilated in the intensive care unit postoperatively, the time to tracheal extubation was used as a surrogate marker of intensive care unit complications and cost. Major complications included myocardial infarction detected by an enzyme rise or electrocardiogram changes, stroke, acute renal failure defined by a rise in serum creatinine to greater than 200 μmol/L or twice the preoperative value, and sepsis defined by new infection or requiring antibiotics.

An estimate of the necessary sample size was based on an anticipated large reduction in the incidence of awareness when using BIS monitoring during general anaesthesia, from 1·0% to 0·1%. A high risk group of patients was identified in order to increase the number of outcome events.[4,6,28] A large treatment effect was modelled because of the extremely low rate of awareness reported with BIS monitoring (0·04%[29]) and because uptake into routine clinical practice would require convincing proof of benefit.[30] Based on a one-sample binomial approximation to Fisher's exact test,[31] we calculated that a total of 12 events needed to be observed to achieve 80% power at 5% two-sided type I error. This value translated into a required recruitment of 1090 patients per group. We planned to recruit 2500 patients to allow for patients dropping out and missing data.

There were three possible mechanisms for early termination of the trial: early evidence of efficacy, early evidence of harm, or insufficient events to reliably detect a true difference. An interim monitoring plan with asymmetric boundaries, guided by the findings of DeMets and colleagues,[32] was used for early evidence of efficacy (two-tailed $p<0·001$) or harm (two-tailed $p<0·017$). An independent data and safety monitoring committee did an interim analysis after 1512 patients had been enrolled. After reviewing the interim results, this committee recommended to the steering committee to continue the trial. The interim data were not revealed to the steering committee. Statistical significance boundaries (two-tailed) at the conclusion of the trial were $p<0·05$ for efficacy and $p<0·041$ for harm.[33]

Group	Sex	Age (years)	Surgery	Reported experience*
RC	F	67	Whipple's procedure	Heard the anaesthetist say "the pressure is really low", and the surgeon respond "can you do something about it?". Recalls movement and pain within the abdomen. Tried to move, but was unable to (1=ND, 2=Y, 3=Y)
RC	M	55	Laparotomy, ruptured hepatoma	Remembers going "half asleep", then hearing shouting ("…do things faster… because things are crashing…"). Felt anxious, dizzy, and breathless, and could not move. Some abdominal pain (1=ND, 2=Y, 3=D)
RC	M	63	Anterior resection	Heard noises during surgery; tried to move but was unable (1=Y, 2=Y, 3=Y)
RC	M	29	Sternotomy, excision of atrial tumour	Heard the sternal saw during surgery, tried to move but was unable (1=Y, 2=N, 3=N)
RC	F	67	Coronary artery surgery	Heard noises and voices during surgery, and the pain of "people trying to tear my chest apart" (1=ND, 2=Y, 3=Y)
RC	M	73	Oesophagectomy	Heard voices, felt something in his chest; tried to move but was unable (1=N, 2=N, 3=Y)
RC	M	66	Valvular and coronary artery surgery	Heard the surgeon talking during surgery (1=ND, 2=Y, 3=N)
RC	M	81	Abdominal aneurysm repair	Heard people shouting during surgery, associated with abdominal "cramps" and pain, like squeezing his gut. He was unable to move and was terrified (1=N, 2=N, 3=Y)
RC	F	77	Embolectomy of axillary artery	After "the needle" (intravenous cannulation), remembers going half-asleep then feeling shaking all over (at the time of suxamethonium), followed by something being passed in her mouth. There was not too much pain. During this time she heard people talking and tried to move, but could not (1=Y, 2=Y, 3=Y)
RC	F	46	Single lung transplant	Heard conversations about war in Afghanistan, recalled her disagreement with the views being put forward; she was unable to move or speak. Also remembered a later time when a suction tube was placed in her throat and someone saying "there are lots of secretions" (a post hoc consultation with the anaesthetist identified this episode occurring during reintubation with a single-lumen tracheal tracheal tube near the end of the procedure); this was uncomfortable (1=Y, 2=Y, 3=Y)
RC	F	41	Heart-lung transplant	Heard the surgeon saying "this is more difficult than expected… [chief surgeon's name] wanted to be called… call for [chief surgeon's name]" (1=ND, 2=ND, 3=Y)
BIS	F	64	Off-pump coronary artery surgery	Heard some voices and the sternal saw during surgery, and had some pain. Heard someone say, "has she had enough anaesthetic?". She did not try to move (1=ND, 2=Y, 3=Y)
BIS	M	64	Laryngoscopy, bronchoscopy, and oesophagoscopy	Recalls a piece of "cold metal" being placed in his mouth; this was slightly painful. Heard some talking and tried to shout, but could not move. This was very brief (1=Y, 2=Y, 3=Y)

RC=routine care. F=female. M=male. Y=yes; N=no; ND=interview could not be done because patient was sedated and intubated in the intensive care unit; D=patient had died. *Parentheses show whether awareness was reported at interviews 1 (about 4 h after surgery), 2 (about 24 h after surgery), and 3 (30 days after surgery).

Table 2: **Summary of confirmed awareness events**

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Statistical analyses

All patients randomised to BIS monitoring or routine care and undergoing surgery were included in the intention-to-treat population for all primary, secondary, and safety analyses. Analysis of the principal outcome of awareness was done with Fisher's exact test. Results were expressed as proportions, odds ratios (OR) with exact 95% CIs accounting for the interim analysis, and p values. Recovery times were compared graphically between groups by Kaplan-Meier survival curves, summarised by median times to event with interquartile ranges, and assessed by the log-rank test and the Cox proportional hazards model for possible covariate adjustment, with assessment of the requisite proportionality assumptions. Other secondary endpoints were analysed using Fisher's exact test or χ^2 tests as above, and the ordinal patient satisfaction scale was assessed using the Wilcoxon rank sum test. All p values are two-sided.

Role of the funding source

The sponsors of the study had no role in the study concept, design, data collection, data analysis, data interpretation, or the writing of the report.

Results

2503 patients were recruited into the trial, but 40 patients were withdrawn because of cancellation of surgery (BIS group 13, routine care group 13), withdrawal of consent (six, two), surgery done without general anaesthesia (four, none), or the patient was under-age (none, two), leaving 2463 patients in the final data set: 1225 patients (49·7%) randomised to the BIS group and 1238 patients (50·3%) to the routine care group (figure 1). Six patients in the routine care group received BIS monitoring mistakenly, and 14 patients were allocated to receive BIS but did not. All these patients were included in their allocated groups for all analyses; none had awareness. 65 patients (BIS group 30, routine care group 35) did not provide any interview data, mainly because of critical illness or death in the postoperative period. The number of patients able to be interviewed at each of the three time periods were: 1531 at 2–6 h (BIS group 764, routine care group 767), 2330 at 24–36 h (1161, 1169), and 2243 at 30 days (1114, 1129).

At baseline, patients' demographics and clinical characteristics were similar in the BIS and routine care groups (table 1). Almost half (45%) of the study population underwent high-risk cardiac surgery, or off-pump coronary artery surgery. Overall, 1272 patients (52%) received their initial postoperative care in the intensive care unit (BIS group 639, routine care group 633).

Until 30 days after enrolment, the number of patients who reported awareness under anaesthesia was significantly smaller in the BIS group than in the routine care group (2 [0·17%] *vs* 11 [0·91%]; OR 0·18; 95% adjusted CI 0·02–0·84; p=0·022); the absolute reduction in the risk of awareness was 0·74%. The number needed to treat (NNT) was 138 (95% CI 77–641). The benefit of

Group	Sex	Age (years)	Surgery	Reported experience
RC	M	62	Open heart surgery	Heard sounds, felt someone punching his chest and felt frightened
RC	M	34	Liver transplant	Felt a large tube being inserted through his nose, heard people say "he is moving", felt weak
RC	F	30	Caesarean section	Dreaming, unable to recall content
RC	F	28	Caesarean section	Dreamt about being in hospital
RC	F	23	Liver lobectomy	Dreamt about aliens and thought aliens had taken over the operation (theatre staff had had a conversation about aliens during surgery)
RC	M	59	Open heart surgery	Heard doctors talking as went off to sleep
RC	M	54	Leg debridement	Heard talking, dreamt about being under anaesthesia
RC	F	41	Heart-kidney transplant	Saw lights above her head and felt anxious; surrounded by relatives, could not touch them
RC	F	47	Dental clearance	Dreamt about her daughter being on an operating table, saw "big light" and felt "stuck in one place", felt tube inserted in throat, could not move, heard conversations
RC	M	72	Open heart surgery	Felt breathless after going off to sleep, felt like "his heart had stopped" and he was "going to die", and that he was a "dead weight"
RC	M	60	Thoracoscopy	Had pain during surgery, dreamt of wife being paralysed
RC	M	59	Off-pump heart surgery	Lying on back, could visualise people around him; heard everyone talking
RC	M	79	Open heart surgery	Dreamt of dying, heard his wife talking, tried to move but was unable
RC	F	59	Liver resection	Woke up with a tube in her mouth, told to close her eyes; dreamed about floating
RC	F	69	Carotid endarterectomy	A nightmare of nurses calling her the wrong name, but patient couldn't talk
RC	M	35	Lumbar discectomy	Heard muffled sounds, vague sense of movement
BIS	F	68	Oesophagectomy	Dreamt about people walking in front of her
BIS	M	49	Open heart surgery	Light flashes, followed by a "nightmare" of being dragged into a black hole
BIS	F	71	Open heart surgery	Lightning flashes, saw doctors examining her chest with a stethoscope
BIS	M	61	Open heart surgery	Heard monitor "beeps", couldn't move
BIS	F	23	Caesarean section	Dreaming, unable to recall content
BIS	F	37	Caesarean section	Dreamt of conversation with friend, but couldn't walk in her garden (in her dream)
BIS	F	41	Caesarean section	Dreaming, unable to recall content
BIS	F	43	Microlaryngoscopy	Felt pressure in throat but no pain, unable to move
BIS	F	21	Pilonidal sinus	Dreamed of having a conversation with the anaesthetist, then heard voice waking her up
BIS	M	39	Laparotomy, ileostomy	Dreamed of car headlights
BIS	M	47	Internal cardioversion	Recalls being extubated and heard "we'll leave that in there for a moment"
BIS	M	41	Heart transplant	Felt tube in throat, heard voices, but could move and saw staff around him (ie, eyes not taped, no surgical drapes)
BIS	M	60	Rigid bronchoscopy	Had a "general awareness of the procedure", but could not recall any specific details
BIS	M	68	Colonic resection	Heard conversation, possibly in intensive care unit,
	F	55	Open heart surgery	Thought she was awake during surgery, but could not remember anything
BIS	M	68	Open heart surgery	Dreamt he was fishing in a boat, and that it sank in a storm
BIS	F	82	Open heart surgery	Felt blood trickling on neck (central venous catheter insertion?), heard voices say "quick, quick"
BIS	M	53	Rigid laryngoscopy	Dreaming, unsure of content
BIS	F	56	Open heart surgery	Perceived a lot of people from her church around her bed, and someone turning her on her side
BIS	M	72	Aortic aneurysm repair	Dreamt of terrible pain and "screaming out" (severe pain had occurred in the recovery room)
BIS	F	77	Hip replacement	Could see overlapping black and white squares

RC=routine care group. M=male. F=female.

Table 3: **Summary of possible awareness events that were not confirmed by the study endpoint committee**

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	BIS group (n=1225)	Routine care group (n=1238)	p*
Induction agents			
Midazolam	760 (62%)	773 (62%)	0·818
Dose (mg)†	2 (2·0–3·5)	2·5 (2·0–4·0)	0·017
Propofol	770 (63%)	775 (63%)	0·916
Dose (mg)†	80 (50–150)	80 (20–150)	0·752
Thiopentone	179 (15%)	189 (15%)	0·643
Dose (mg)†	250 (175–375)	250 (200–375)	0·845
Nondepolarising muscle relaxant	1145 (93%)	1172 (95%)	0·179
Suxamethonium	269 (22%)	270 (22%)	0·919
Total intravenous anaesthesia	532 (43%)	523 (42%)	0·553
Infusion rate (mg/kg per h)†	5 (4–6; n=172)	5 (3–6; n=165)	0·384
Target plasma concentration (mg/L)†	2 (2–3; n=352)	2·4 (2–3; n=357)	0·016
Nitrous oxide	433 (35%)	461 (37%)	0·329
Opioid dose			
Fentanyl (mg)†	500 (100–1000; n=863)	600 (100–1175; n=840)	0·661
Morphine (mg)†	10 (7–15; n=433)	10 (7–15; n=506)	0·938
End-tidal volatile concentration (MAC equivalents)†‡	0·57 (0·43–0·72)	0·61 (0·43–0·78)	0·169
Hypnotic drug administration stopped for >5 min	91 (7%)	80 (6%)	0·345
Combined general and regional anaesthesia	216 (18%)	189 (15%)	0·113
Marked hypotension			
All cases	717 (58%)	694 (56%)	0·215
Non-bypass§	433 (50%)	393 (45%)	0·049

*p values derived from either χ^2 test or a Mann-Whitney *U* test. †Data are median (IQR), with n if different from group total; other data are number (%). ‡MAC=minimum alveolar concentration, a measure of anaesthetic volatile agent potency; the MACs of sevoflurane, isoflurane, enflurane, and halothane are 1·80, 1·15, 1·7, and 0·75, respectively. §Excluding patients undergoing cardiac surgery with cardiopulmonary bypass (n=735)

Table 4: **Comparison of anaesthetic procedures**

BIS monitoring was altered little in an analysis adjusted for age, sex, and cardiac surgery (adjusted odds ratio, 0·18; p=0·02, with exact logistic regression).

There were 22 reports of confirmed or possible awareness in the BIS group (1·8%) and 27 reports in the routine care group (2·2%; p=0·49). A brief description of the confirmed episodes of awareness is provided in table 2. The two episodes of awareness in the BIS group occurred at BIS readings of 79–82 and 55–59. In these cases a BIS reading greater than 60 occurred for 5 min and 9 min, respectively. These episodes of awareness in the BIS group occurred at a time when the BIS readings were high compared with the BIS data for the entire group. If patients recalling intraoperative events but not the pain of surgery were excluded, leaving two patients in the BIS group and nine in the routine care group, there was no significant effect on risk reduction (OR=0·22; 95% CI 0·02–1·08; p=0·065). If incidents of awareness during intubation were excluded, leaving one patient in the BIS group and ten in the routine care group, the risk reduction was greater (0·10; 0·002–0·70; p=0·012).

There were 62 reports of intraoperative dreaming in the BIS group (5·2%) and 83 reports in the routine care group (6·9%; p=0·079). In addition to the confirmed episodes, there were 36 reports of possible awareness that were not confirmed by the study endpoint committee (20 patients in the BIS group *vs* 16 in the routine care group; p=0·50), most of which involved vivid dreaming about subject matter unrelated to surgery (table 3). Some reports described sounds, touch, or pain, but it was uncertain as to when the event occurred—for example, the endpoint committee judged that some events could have occurred during the time spent in the intensive care unit.

In the BIS group the time-averaged BIS reading throughout the procedure was 44·5 (SD 6·8, median 44, IQR 40–49). The lowest BIS reading persisting for at least 5 min was 33·6 (9·6, 35, 30–40); the highest BIS reading persisting for at least 5 min was 55·5 (9·8, 55, 48–61). The mean duration of BIS greater than 60 was 3·6 min (13·4; 0, 0–4). Of the 1227 patients in the BIS group, 650 received anaesthesia with the BIS below 60 at all times. Of the 14 patients allocated to BIS monitoring that did not receive it, none had an episode of awareness or possible awareness.

The choice of anaesthesia technique, drugs, and duration of administration were generally similar in the BIS and routine care groups (table 4). The exceptions were the dosage of midazolam used at induction of anaesthesia, and the target concentration of propofol used for total intravenous anaesthesia, which were less in the BIS group than in the routine care group (table 4).

Of the 1123 patients admitted to the post-anaesthesia care unit, those in the BIS group recovered faster from anaesthesia, as measured by time to eye opening. The median time to eye opening was 9 min in the BIS group and 10 min in the routine care group (p=0·003). A proportional hazards regression gave a hazard ratio of 1·19 for BIS compared with routine care (95% CI 1·06–1·34). The hazard ratio was unaffected by adjustment for age and duration of surgery (hazard ratio 1·20, p=0·004). The time to discharge from the post-anaesthesia care unit was similar between groups, (hazard ratio 1·07; 95% CI

	BIS group (n=1225)	Routine care group (n=1238)	p*
Destination of patients after surgery			0·218
PACU	547 (45%)	576 (47%)	
High-dependency unit	37 (3%)	25 (2%)	
ICU	639 (52%)	633 (51%)	
Patients admitted to PACU			
Time to eye opening (min)†	9 (5–14)	10 (5–15)	0·003
Time to discharge (min)†	63 (40–95)	66 (40–100)	0·265
Patients admitted to ICU			
Time to tracheal extubation (h)†	10·8 (5·9–20·2)	10·2 (6·3–19·3)	0·893
Patients' satisfaction			
At 24 h (n with data)	1161	1169	0·539
Very satisfied	773 (67%)	764 (65%)	
Satisfied	336 (29%)	350 (30%)	
Somewhat or less than satisfied	52 (5%)	55 (5%)	
At 30 days (n with data)	1126	1150	0·528
Very satisfied	751 (67%)	781 (68%)	
Satisfied	328 (29%)	324 (28%)	
Somewhat or less than satisfied	47 (4%)	45 (4%)	
HAD scale at 30 days‡			
Anxiety score†	3 (1–6; n=1108)	3 (1–6; n=1127)	0·964
Depression score†	3 (1–6; n=1033)	3 (1–6; n=1010)	0·677
Postoperative complications			
Myocardial infarction	54 (4·4%)	52 (4·2%)	0·796
Stroke	15 (1·2%)	18 (1·5%)	0·621
Acute renal failure	49 (4·0%)	55 (4·5%)	0·585
Sepsis	222 (18·3%)	221 (18·0%)	0·860
Death	51 (4·2%)	50 (4·1%)	0·873
Any of the above	283 (23·2%)	288 (23·4%)	0·934

PACU=post-anaesthesia care unit. ICU=intensive care unit. Data are number (%) unless otherwise stated. *Log rank test for time-to-events, Mann-Whitney test for continuous data, χ^2 test for categorical data. †Data are median (IQR). ‡HAD=hospital anxiety and depression scale (range 0 [lowest level] to 21).

Table 5: **Recovery times and postoperative complications**

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0·95–1·20; p=0·28). After adjustment for age and duration of surgery the hazard ratio increased slightly to 1·11 (p=0·09).

Similar proportions of patients were admitted to the intensive care unit (p=0·22; table 5). BIS monitoring had no significant effect on the time to tracheal extubation in patients admitted to the intensive care unit. The median time to tracheal extubation for the BIS group was 10·8 h and for the control group was 10·2 h (hazard ratio 0·99; p=0·89). An additional 62 patients were treated in a high-dependency environment, but did not need ongoing tracheal intubation or mechanical ventilation.

Neither death nor postoperative complications showed any significant differences between the groups (table 5). Patients' scores for satisfaction, anxiety, and depression after surgery were similar between groups (table 5). The anxiety and depression scores at 30 days postoperatively between those who had confirmed awareness and those without awareness were similar for anxiety (p=0·06) and depression (p=0·27). Patients with confirmed awareness reported lesser satisfaction than those without confirmed awareness at both the 24 h and 30 day interviews (p<0·0001 for both).

Discussion

In this study, BIS monitoring reduced the risk of awareness by 82% in at-risk adults undergoing relaxant general anaesthesia. BIS monitoring had little effect on the time needed to recover from general anaesthesia, as measured by eye opening, and no measurable effect on the risks of postoperative complications. Our findings confirm previous observational data suggesting that awareness during BIS monitoring is less common than during routine care.[29] Some patients could not be interviewed at each planned time because they were still sedated and intubated in the intensive care unit; others did not recollect their awareness at all three interviews, as has been previously described.[3]

Awareness results from an imbalance between anaesthetic need and delivery. During any surgical procedure, the intensity of surgical stimulation, and thus anaesthetic need, varies greatly. Additionally, some patients might have unpredictably high anesthetic requirement. On the other hand, anaesthetic delivery may be constrained by concerns about fetal wellbeing or haemodynamic side-effects of the anaesthetic drugs. Alternatively, insufficient anaesthesia can be delivered as a result of technical errors or equipment failure.[34-36] Previously, anaesthetists have been unable to directly monitor the balance between need and delivery.

The study population comprised patients in whom imbalances between need and delivery were likely to arise.[4-6] Previous studies predicted an incidence of awareness of about 1% in this high-risk group, so we expected about 12 patients undergoing routine anaesthesia care to suffer awareness.[4-6] Our findings were in accord with this prediction, despite concern that participation in the study might reduce the observed rate of awareness by a Hawthorne effect. Some evidence suggests that anaesthetists treated patients differently if they were allocated to routine care, since higher doses of midazolam and propofol, drugs with known amnesic properties, were administered to this group, suggesting that there was a concern about awareness. Additionally, the time taken to recover from anaesthesia, as measured by the time to eye opening, was slightly longer in the routine care group. The clinical significance of this difference is slight but it does show that anaesthesia was maintained at a deeper level in the routine care group, with a resultant delay in early recovery. Anaesthetists vary in the way they reduce anaesthetic drug administration towards the end of surgery; some discontinue administration before or during wound dressing, while others wait until wound dressing is complete. Variation in the timing of the starting point of the recovery process could have had an effect on the results, especially in relation to the time to eye opening, which was only a few minutes after the end of surgery. We judged that the only clear and consistent way to define the start of recovery was as the moment when anaesthesia was no longer needed: when wound closure was complete. Anaesthetists treating patients in the BIS group might have preferentially reduced anaesthetic drug administration at an earlier time, which would introduce a source of bias. A reduction in recovery times with BIS-guided anaesthesia has been shown previously.[18,22] However, despite less hypnotic drug administration, we noted no reduction in the incidence of hypotension; an apparent increased incidence in non-bypass cases could be real or a spurious finding attributable to multiple testing (type I error).

Two patients in the BIS-guided group had an episode of awareness. One patient had a brief recollection of rigid laryngoscopy that was slightly painful, and happened at a time when the BIS reading was recorded at 79–82. This value should have indicated that anaesthesia was insufficient and any painful procedure abandoned until adequate anaesthesia was provided. This incident does not indicate a failure of BIS monitoring, but does show that vigilance and action by the anaesthetist is needed to gain the benefits that such monitoring can provide. Routine setting of alarm limits for BIS values outside the recommended range should assist the anaesthetist in such instances. The second patient heard voices and the sternal saw at the beginning of off-pump coronary artery surgery, when the BIS readings were in the range 55–59. This episode suggests that awareness can arise when the BIS is at the upper limit of the recommended (40–60) range. This finding is consistent with the underlying derivation of the BIS,[11,17] whereby several electroencephalograph variables are used to calculate a probability of patient wakefulness (explaining why most patients with a BIS of 60–70 will not be aware). A response to this one case might be to ensure that the BIS is less than 55 if awareness is to be avoided in most cases. Such a view remains speculative and warrants further investigation. As with previous studies,[3,7-9] there were several reports of awareness without recollection of the pain of surgery. Most anaesthetists and their patients regard such recollections as true awareness, and such experiences can lead to long-term distress.[7-10]

Intraoperative dreaming was not uncommon, and similar rates have been reported previously.[4] It is unclear whether this represents a light level of anaesthesia analogous to near-awareness. The identification and interpretation of possible awareness is problematic, because the differentiation between dreaming, awareness, and recollection of events in the early postoperative period can be vague. We noted no difference in the rates of awareness when all reports from patients were included in the analysis, including 36 reports that were not deemed to represent awareness by our blinded endpoint committee. This finding highlights the need to investigate and scrutinise all reported recollections, and to reassure patients that intraoperative dreaming and recollection of events during emergence from anaesthesia are not uncommon.

Our trial tested the effectiveness of BIS monitoring in a real-world setting, and therefore its results can be generalised. Nevertheless, our study population was restricted to those judged to be at increased risk of awareness, and so the results might not apply to all patients undergoing relaxant general anaesthesia. The NNT to avoid an episode of awareness in this high-risk group was

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138. At an acquisition cost of BIS monitoring of US$16 per surgical procedure in Australia (range $15–28 worldwide), the cost of preventing one case of awareness in a high-risk population is about US$2200.

The acceptance of an awareness monitor by anaesthetists not only rests on evidence of effectiveness, but also on their perception of the importance of awareness.[37] For patients, awareness is a significant source of anxiety about, and dissatisfaction with, anaesthesia care.[2,38] Additionally, an episode of awareness can result in serious, long-lasting morbidity, including post-traumatic stress disorder.[8-10,34]

In conclusion, we have shown that use of BIS monitoring can reduce the incidence of awareness under general anaesthesia in patients at risk, suggesting that greater use of BIS monitoring is warranted in patients at increased risk of awareness undergoing relaxant general anaesthesia.

B-Aware trial group

Steering Committee: P Myles (Alfred Hospital, Melbourne, Australia), K Leslie (Royal Melbourne Hospital), J McNeil (Monash University). Data and Safety Monitoring Committee: K Jamrozik (Imperial College Faculty of Medicine, London, UK), J Rigg (University of Western Australia), G Ludbrook (Royal Adelaide Hospital, University of Adelaide), A Forbes (Monash University). Endpoint Adjudication Committee: M Langley (Alfred Hospital), G Downey (Alfred Hospital), R McRae (Monash Medical Centre). Biostatisticians: A Forbes, R Wolfe (Monash University). *The B-Aware trial group included*: T Short, R Fry (Auckland Hospital, Auckland, New Zealand); P McLoughlin, M Paech (Royal Perth Hospital, Western Australia); M Beaudoin (Prince of Wales Hospital, New South Wales, Australia); P Peyton (Austin Hospital, Victoria, Australia); A Plowman (Geelong Hospital, Victoria, Australia); N Warwick, M Priestley (Westmead Hospital, New South Wales, Australia); B Law (Kwong Wah Hospital, Hong Kong); S Valentine (Fremantle Hospital, Western Australia); T McCulloch (Royal Prince Alfred Hospital, New South Wales, Australia); S Swallow (Royal Hobart Hospital, Tasmania, Australia); J Fabling (Charles Gairdner Hospital, Western Australia); P Kam, S Barratt (Royal North Shore Hospital, New South Wales, Australia); B Silbert (St Vincent's Hospital, Victoria, Australia); J Monagle (Dandenong Hospital, Victoria, Australia); A Lilley, A Buettner (Royal Women's Hospital, Victoria, Australia); R Ray, G Hughes (Ballarat Base Hospital, Victoria, Australia); D Sutton (Monash Medical Centre, Victoria, Australia); T Vaughan (Flinders Medical Centre, South Australia); V Jiranantarat (Suriraj Hospital, Thailand); A Morley (St Thomas' Hospital, London, UK); S Gatt (Royal Hospital for Women, New South Wales, Australia).

Contributors

The study was designed by P Myles, K Leslie, J McNeil, and A Forbes. P Myles co-ordinated the study and A Forbes did the statistical analysis. P Myles, K Leslie, A Forbes, and M Chan were the writing committee.

Conflict of interest statement

The trial received loan equipment and some unrestricted funding from Aspect Medical Systems (Newton, MA, USA). K Leslie has received support for travel and conference expenses from Aspect Medical Systems. None of the other authors has declared any conflict of interest.

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