Reviewer 1: JS **Reviewer 2: GF**

Reference and design	*Technology*	*Participants*	*Outcome measures*
Author: Aime *et al.*[61] **Year:** 2006 **Study design:** RCT **Number of centres:** one **Country:** France **Sponsor:** GE Healthcare Monitoring Solutions loaned the authors a S5 monitor and provided the probes. No other funding source reported **Trial name:** NR	**Group 1:** BIS (Version 4.0 XP, Aspect Medical Systems), using Datex-Ohmeda S/5™ monitor Target device/ index value: 40–60 Commencement of monitoring: started in the operating room. Not stated when monitoring ceased **Group 2:** Entropy module (GE Healthcare) using Datex-Ohmeda S/5™ monitor Target device/ index value: response entropy and state entropy 40–60. Intermittent bolus doses of sufentanil given if response entropy–state entropy difference >10 for >2 minutes Commencement of monitoring: started in the operating room. Not stated when monitoring ceased **Group 3:** Standard practice (routine clinical signs) Hypertension/ hypotension, tachycardia Length of experience/ training of anaesthetist: described as 'more than 3 months of routine use'	**Total numbers involved:** $n = 140$; group 1, $n = 40$; group 2, $n = 40$; group 3, $n = 60$ Premedication used: 100 mg hydroxyzine orally 1 hour before surgery General anaesthetic used: i.v. propofol 2–3 mg/kg (induction). Sevoflurane in 60% nitrous oxide with oxygen Regional anaesthesia used: none Analgesia used: i.v. sufentanil 0.2–0.3 µg/kg injected over 15–30 seconds (induction), 0.15–0.20 µg/kg/hour with 5 µg bolus given 5 minutes before surgical incision. Intravenous morphine for postoperative analgesia started approximately 20 minutes prior to scheduled end of surgery (0.1–0.15 mg/kg), plus paracetamol, nefopam, non-steroidal anti-inflammatory drugs Muscle relaxants used: i.v. atracurium 0.5 mg/kg Antinausea drugs used: not stated Other drugs used: esmolol (for tachycardia), nicardipine 1–2 mg (hypertension), ephedrine 3–6 mg i.v./ phenylephrine 20–100 µg i.v. (for hypotension), atropine 0.5 mg i.v. (bradycardia) Type of surgery: abdominal; gynaecological, urological, orthopaedic Duration of surgery: precise duration not stated. Minimum 1 hour Duration of GA: ranged from 170.8 (± 90.6) minutes (standard practice group) to 190.8 (± 84.9) minutes (spectral entropy-guided group) **Inclusion criteria:** aged 18–80 years, ASA physical status I, II, III, scheduled for elective abdominal, gynaecological, urological or orthopaedic surgery expected to last at least 1 hour **Exclusion criteria**: history of any disabling central nervous or cerebrovascular disease, hypersensitivity to opioids or substance abuse, treatment with opioids or any psychoactive medication, or a body weight <70% or more than 130% of ideal body weight **Baseline measurements:** Sex (male), *n* (%): group 1 = 14 (41); group 2 = 23 (62%); group 3 = 23 (43%) Age years, mean (SD): group 1 = 57;(± 19); group 2 = 58 (± 18); group 3 = 54 (± 15) Ethnic groups, *n* (%): NR Weight kg: group 1 = 73 (± 18.2); group 2 = 77.6 (± 17.3); group 3 = 68.8 (± 13.4) ASA grade, *n* (I/II/III): group 1 = 13/16/5; group 2 = 14/19/4; group 3 = 26/24/4 Risk factors for awareness: none reported **Comorbidities:** none reported **Losses to follow-up:** none reported **Place of anaesthetic administration:** operating room	**Primary outcome:** • Reduction in sevoflurane consumption **Secondary outcomes:** • Sufentanil consumption • BIS and E-Entropy device values • Haemodynamic profiles (bradycardia, tachycardia, normal range of arterial blood pressure) • Treatment of adverse events (hypotension/ hypertension/ tachycardia/ bradycardia) • % of time passed with hypotension/ hypertension/ tachycardia/ bradycardia • Time to spontaneous eye opening • Time to extubation • Intraoperative recall **Length of follow-up**: intraoperative recall assessed on first and third postoperative days **Methods of assessing outcomes:** sevoflurane consumption measured by sevoflurane vaporiser weight: mean for one patient; mean for one patient normalised to the duration of anaesthetic; mean for one patient normalised to the duration of anaesthetic and also to the weight of the patient Intraoperative recall measured by standardised interview (Brice *et al.*[24])

NR, not reported; SD, standard deviation.

Outcome	Group 1	Group 2	Group 3	*p*-value
Intraoperative awareness/recall	0	0	0	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR	NR
Time to spontaneous eye opening (minutes)	7.6 (± 4.1)	7.2 (± 4.7)	8.0 (± 3.9)	NR
Time to extubation (minutes)	11.1 (± 5.1)	11.5 (± 5.8)	14.2 (± 9.0)	NR
Time to discharge to/from the recovery room	NR	NR	NR	NR
Anaesthetic consumption (for one patient) mean (SD)				
Sevoflurane consumption (g)	21.3 (± 11.1)	22.8 (± 14.4)	25.6 (± 17.2)	0.49
Sevoflurane consumption normalised (g/hour)	7.2 (± 3.0)	7.8 (± 3.4)	9.4 (± 5.6)	0.07
Sevoflurane consumption normalised (g/kg/hour)	0.10 (± 0.04)	0.10 (± 0.05)	0.14 (± 0.09)	0.003
HRQoL	NR	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR	NR
Pain/pain relieving drugs (for one patient)				
Sufentanil induction dose				
Sufentanil induction dose (μg/kg)	0.22 (± 0.05)	0.21 (± 0.05)	0.23 (± 0.06)	0.18
Sufentanil induction dose (μg/hour)	14.0 (± 6.7)	13.6 (± 6.1)	14.9 (± 8.3)	0.66
Sufentanil maintenance consumption (μg/kg/hour)	0.20 (± 0.09)	0.18 (± 0.09)	0.22 (± 12)	0.26
Other morbidity				
Ephedrine use (*n*)	3	2	4	NR
Nicardipine use (*n*)	1	2	2	NR
Esmolol	0	0	1	NR
Atropine (*n*)	1	0	0	NR
Mortality	NR	NR	NR	NR

NR, not reported; SD, standard deviation.

Additional results/comments (e.g. early response factors, QoL)

Percentage of time passed (induction, maintenance, recovery and total) with bradycardia (<75% of baseline values), normal range of heart rate, tachycardia (>125% of baseline values), hypotension (<75% of baseline values), normal range of mean arterial blood pressure, and hypertension (>125% of baseline values) were similar among groups (data not extracted)

Results demonstrate that BIS and spectral entropy guidance for the titration of sevoflurane results in a reduction of 29% in sevoflurane consumption

Sevoflurane consumption was statistically significantly different between study arms only when normalised for patient weight and duration of anaesthesia

Methodological comments

Allocation to treatment groups: random using a randomisation list performed with computer-generated random numbers

Allocation concealment: NR

Blinding: NR

Analysis by ITT: analysis excluded those who became ineligible post randomisation

Comparability of treatment groups at baseline: reported to be similar in demographics except that patients in the E-Entropy-guided group (group 2) were statistically significantly heavier ($p = 0.04$). More males were included in the E-Entropy-guided group

Method of data analysis: chi-squared test for nominal data. One-way analysis of variance with Bonferroni's test for multiple comparisons used for numerical data

Sample size/power analysis: previous open study from the authors' institution in the same surgical population showed that sevoflurane consumption was 0.16 ± 0.10 g/kg/hour. Applying an a priori power analysis, at least 34 patients had to be enrolled in each treatment group to detect a reduction of 50% in the sevoflurane consumption with a risk α of 0.05 and a statistical power of 0.9. The authors included 60 patients in the standard practice group and 40 in the BIS and spectral E-Entropy-guided groups

Attrition/dropout: six patients excluded from group 3 (one not extubated at the end of surgery due to hypothermia, three required intraoperative propofol administration, and missing data in two cases), six patients excluded from group 1 (three not extubated at the end of surgery because of hypothermia, two required intraoperative propofol administration, and monitor data were lost in one case), and three from group 2 (all were not extubated at the end of surgery because of hypothermia, two required intraoperative propofol administration)

General comments

Generalisability: general surgical population receiving an inhaled maintenance anaesthetic, not specifically identified as at increased risk for intraoperative awareness

Intercentre variability: NA

Conflict of interests: none declared. Some of the monitoring equipment used was provided by GE Healthcare

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Computer-generated randomisation
Allocation concealment	Unclear	No information given
Performance bias		
Blinding of participants and personnel	Unclear	No information given
Detection bias		
Blinding of outcome assessment	Unclear	No information given
Attrition bias		
Incomplete outcome data	Low	Exclusions generally balanced between groups, and generally similar reasons given
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

Reviewer 1: JS	Reviewer 2: GF		
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Avidan[44] Year: 2011 **Study design:** RCT **Number of centres:** three **Countries:** USA/Canada **Sponsors:** Foundation for Anaesthesia Education & Research; American Society of Anaesthetists Winnipeg Regional Health Authority & University of Manitoba Department of Anaesthesia; Department of Anaesthesiology at Washington in St. Louis; University; Department of Anaesthesiology at University of Chicago **Trial name:** BIS or Anaesthetic Gas to Reduce Explicit Recall trial (BAG-RECALL)	**Group 1:** BIS (Covidien) Target device/index value: 40–60 (audible alarms used outside of this range) **Group 2:** ETAC (audible alarms used outside of 0.7 to 1.3 age-adjusted MAC range in group 2 only) Patients in group 2 had monitors configured to conceal the BIS value and did not receive a BIS audible alarm Commencement of monitoring: not stated Length of experience/training of anaesthetist: summaries of BIS and ETAC protocols were given to the practitioners to provide education and to increase adherence. Signs were affixed to anaesthesia machines to remind practitioners to check BIS/ETAC and consider patient awareness	**Total numbers involved:** 6041 randomised; 3021 (group 1); 3020 (group 2) Premedication used: midazolam used in 80.8% patients (group 1); 79.7% of patients (group 2) General anaesthetic used: isoflurane, sevoflurane or desflurane (further information not reported) Regional anaesthesia used: none (except for 13 patients who were excluded from the study) Analgesia used: not stated Muscle relaxants used: not stated Antinausea drugs used: not stated Other drugs used: not stated Type of surgery: not explicitly reported, but inclusion criteria refer to open heart surgery (see below) Duration of surgery: not stated Duration of GA: not stated **Inclusion criteria:** 18 years or older, undergoing GA with isoflurane, sevoflurane or desflurane. At high risk for intraoperative awareness for one or more of the following risk factors: planned open heart surgery; aortic stenosis; pulmonary hypertension; use of opiates; use of benzodiazepines; use of anticonvulsant drugs; daily alcohol consumption; ASA status 4; end-stage lung disease; history of intraoperative awareness; history of or anticipated difficult intubation; cardiac ejection fraction <40%; marginal exercise tolerance **Exclusion criteria:** patients with dementia, unable to provide written informed consent, or had a history of stroke with residual neurological deficits. 'Minor risk factors' for awareness as used in the B-Aware study were not used as enrolment criteria **Baseline measurements:** Sex (male), *n* (%): group 1 = 1621 (56.7); group 2 = 1679 (58.9) Age years, mean (SD): group 1 = 60 (± 14.2); group 2 = 61 (± 14.4)	**Primary outcome:** • Incidence of definite intraoperative awareness **Secondary outcomes:** • Definite or possible awareness (pre-specified secondary outcome) • Distressing experience of awareness (post hoc secondary outcome) **Length of follow-up:** up to 30 days post extubation **Methods of assessing outcomes:** awareness assessed by modified Brice questionnaire (references cited). Assessments made 72 hours after surgery, and 30 days after extubation. Patients who reported memories of the period between 'going to sleep' and 'waking up' were contacted by a different evaluator, who asked additional structured questions. Three experts independently reviewed responses to the questionnaire from patients who had reported memories and determined whether the reported event involved definite awareness, possible awareness or no awareness. Experts assigned each event of definite or possible awareness to one of the categories of the Michigan Awareness Classification Instrument. In the event of divergence of opinion a fourth expert reviewer who reviews cases for the Anaesthesia Awareness Registry of the ASA, made the final determination

Reviewer 1: JS	Reviewer 2: GF		
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Ethnic groups, *n* (%): White: group 1 = 2405 (84.1); group 2 = 2388 (83.7) Black: group 1 = 357 (12.5); group 2 = 369 (12.9) Other: group 1 = 99 (3.5); group 2 = 95 (3.3) Weight BMI (SD): group 1 = 30 (± 8.4); group 2 = 30 (± 8.3) ASA grade, *n* (%): 1: group 1 = 23 (0.8); group 2 = 19 (0.7) 2: group 1 = 468 (16.4); group 2 = 407 (14.3) 3: group 1 = 1416 (49.5); group 2 = 1407 (49.3) 4: group 1 = 954 (33.3); group 2 = 1019 (35.7) Composite number of inclusion criteria met (risk factors as defined above under 'inclusion criteria') • Median: 2 (group 1); 2 (group 2) • Interquartile range: 1–3 (group 1); 1–3 (group 2) Comorbidities: Composite number of pre-existing medical conditions (as above) • Median: 2 (group 1); 2 (group 2) • Interquartile range: 1–3 (group 1); 1–3 (group 2) **Losses to follow up:** 46 (group 1); 50 (group 2) **Place of anaesthetic administration:** NR	

NR, not reported; SD, standard deviation.

Outcome	Group 1	Group 2	Difference, BIS-ETAC percentage points (95% CI)	*p*-value
Intraoperative awareness, *n/N* (%)				
Definite	7/2861 (0.24)	2/2852 (0.07)	0.17 (–0.03 to 0.38)	0.98
Definite or possible	19/2861 (0.66)	8/2852 (0.28)	0.38 (0.03 to 0.74)	0.99
Patient distress and sequelae resulting from perioperative awareness, *n* (%)	8/2861 (0.28)	1/2852 (0.04)	0.24 (0.04 to 0.45)	0.99
Time to emergence from anaesthesia	NR	NR	NR	NR
Time to extubation	NR	NR	NR	NR
Time to discharge to/from the recovery room	NR	NR	NR	NR
Anaesthetic consumption	NR	NR	NR	NR
HRQoL	NR	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR	NR
Mortality				
Died before first interview	33/2907 (1.14%)	38/2902 (1.31%)	NR	NR
30-day mortality	57/2907 (1.96%)	64/2902 (2.21%)	0.24 (–0.50 to 0.99)	NR

NR, not reported.

Additional results/comments

In total, 49 patients, including patients from all three enrolment sites, reported having memories of the period between 'going to sleep' and 'waking up' at the end of surgery

Experts determined that nine patients had definite intraoperative awareness (incidence 0.16%, 95% CI 0.08 to 0.30), and 27 patients had definite or possible awareness (incidence 0.47%, 95% CI 0.32 to 0.68)

A classification of awareness events is given, according to the Michigan Awareness Classification (data not extracted)

Patients who experienced awareness compared with patients who did not, met a median of one additional inclusion criterion and had a median of one additional pre-existing medical condition

A total of five of the nine patients who experienced possible awareness did not have either BIS values of >60 or ETAC values of <0.7 age-adjusted MAC

Overall, during the maintenance of anaesthesia the BIS was <60, a median of 94.0% of the time (interquartile range, 93.6–100), and the ETAC was >0.7 age-adjusted MAC, a median of 84.8% of the time (interquartile range, 67.2–95.3)

In both groups the median length of stay in the hospital was 7.0 days, and the median length of stay in the ICU was 2.1 days

There were no important differences between the groups in the doses of sedative, hypnotic, opioid analgesic or neuromuscular-blocking drugs administered

Methodological comments

Allocation to treatment groups: 6100 pre-randomisation designations were generated electronically *n* blocks of 100, divided equally between the groups

Allocation concealment: labels indicating BIS group or ETAC group were sealed in opaque, numbered envelopes

Blinding: the anaesthesia practitioners were aware of the patients' group assignments, but the patients, the postoperative interviewers, the expert reviewers and the statisticians were not

Analysis by ITT: a modified ITT analysis was performed, which included all patients who underwent randomisation and who were assessed for intraoperative awareness. All the patients were treated with the protocol to which they had been randomly assigned

Comparability of treatment groups at baseline: Statistically significant differences were found for two variables: use of anticonvulsant drugs (slightly higher in group 1); cardiac ejection fraction <40% (slightly higher in group 2)

Method of data analysis: Fisher's exact test for primary and secondary analysis. Chi-squared test, Fisher's exact test, unpaired Mann–Whitney *U*-test or unpaired Student's *t*-test used for other comparisons

Sample size/power analysis: it is estimated that with 6000 patients the study would have 87% power to detect a clinically significant reduction of 0.4 percentage points in the incidence of definite awareness with the BIS protocol, compared with the ETAC protocol (from 0.5% in the ETAC group to 0.1% in the BIS group), at a one-tailed alpha level of 0.05 with the use of Fisher's exact test

Attrition/dropout: of the 3021 patients randomised to group 1, 114 (3.8%) were excluded post randomisation. Of the remaining 2907 patients, 46 (1.6%) were lost to follow-up and 2861 were assessed for intraoperative awareness. Of the 3020 patients randomised to group 2, 118 (3.9%) were excluded. Of the remaining 2902, 50 (1.7%) were lost to follow-up and 2852 were assessed for intraoperative awareness. Reasons given for exclusions and loss to follow-up in both groups were similar (primarily death before awakening). 5713 (98.3%) completed at least one postoperative interview and were included in the primary outcome analysis. 5413 (93.2%) completed the postoperative interviews at both times (within 72 hours after surgery and at 30 days after extubation)

General comments

Generalisability: surgical population classified at high risk of intraoperative awareness receiving inhaled anaesthesia. Not applicable to the general surgical population, and those receiving i.v. anaesthesia. BIS and ETAC were used as part of structured protocols. It was not the intention of the protocols to prescribe or restrict the use of anaesthetic agents. Practitioners could decrease anaesthetic administration at their discretion if a patient's condition was haemodynamically unstable. The protocols were designed to increase vigilance and to provide warnings that patients might be aware

Intercentre variability: median BIS and ETAC values were similar between the three study sites

Conflict of interests: states that no potential conflict of interest was reported

Domain	Author's judgement (state: low/high/unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Electronic randomisation
Allocation concealment	Low	Sealed opaque envelopes
Performance bias		
Blinding of participants and personnel	Unclear	
Detection bias		
Blinding of outcome assessment	Low	Postoperative interviewers, the expert reviewers and the statistician were not aware of group assignment
Attrition bias		
Incomplete outcome data	Low	Level of missing data from postrandomisation exclusions and loss to follow-up and reasons were similar between study arms
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

Reviewer 1: GF Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Bannister *et al.*[45] **Year:** 2001 **Study design:** RCT **Number of centres:** not reported; appears to be one **Country:** USA **Sponsor:** supported in part by a grant from Aspect medical systems (device manufacturer)	**Group 1:** BIS (version 3.3, Aspect Medical Systems) using an A-1050 EEG monitor Target device/ index value: 40–60 during maintenance and 60–70 during last 15 minutes of surgery Commencement of monitoring: prior to anaesthesia; location not reported **Group 2:** standard practice (at anaesthesiologist's discretion using unspecified clinical signs and haemodynamic changes). BIS was recorded but the anaesthesiologist was blinded to BIS data Length of experience/training of anaesthetist: NR	**Total numbers involved:** $n = 75$; group 1, $n = 40$, group 2, $n = 35$ NB part of a wider study (total $n = 202$) that included patients aged 0–3 years and 3–18 years, with patients randomised within age groups. Only the 3- to 18-years age group meets the systematic review age inclusion criterion and is reported here (mean age in the younger group ≤2.2 years) Premedication used: midazolam 0.3–0.75 mg/kg (group 1, 77.5%, group 2, 88.6%) General anaesthesia (induction and maintenance): sevoflurane in 60% N_2O in oxygen (8% sevoflurane in induction; not stated for maintenance) Regional anaesthesia: none Analgesia: fentanyl 1–2 µg/kg or morphine 0.05–0.1 mg/kg Muscle relaxants: non-polarising i.v. neuromuscular block (no other details) Antinausea drugs: none reported Other drugs: opioids (dose not specified) Type of surgery: tonsillectomy and/or adenoidectomy Duration of surgery, mean ± SD: group 1, 27.7 ± 17.1 minutes; group 2, 33.2 ± 20.3 minutes Duration of GA: not reported **Inclusion criteria:** not reported other than age 6–18 years and undergoing tonsillectomy and/or adenoidectomy **Exclusion criteria:** NR Baseline measurements: Sex (male), *n* (%): group 1, 26 (65.0); group 2, 23 (65.7) Age (years), mean ± SD: group 1, 6.7 ± 2.5; group 2, 6.1 ± 2.6 Ethnic groups, *n* (%): NR Weight (kg), mean ± SD: group 1, 26.9 ± 10.6; group 2: 27.7 ± 14.7 ASA grade: NR Risk factors for awareness: none reported Comorbidities: none reported **Losses to follow-up:** none reported **Place of anaesthetic administration:** NR	**Outcomes (not reported whether primary or secondary):** • Sevoflurane consumption • BIS device values • Time to first movement response • Time to extubation • Time to PACU discharge • Haemodynamic parameters (mean arterial pressure and heart rate) **Length of follow-up:** limited to period up to discharge from PACU **Methods of assessing outcomes:** sevoflurane concentration was measured with a Capnomac Ultima gas analyser (Datex Medical Instrumentation Inc., Helsinki, Finland) and end-tidal concentration was continuously recorded by a computer PACU discharge readiness was defined as a score of ≥12, with no zeros, on a modified Aldrete scale and in a room air O_2 saturation ≥94%

NR, not reported.

Outcome	Group 1: BIS ($n = 40$)	Group 2: Standard clinical practice ($n = 35$)	p-value
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia: mean ± SD time to first movement response, minutes	4.2 ± 3.7	7.0 ± 3.9	<0.05
Mean ± SD time to extubation, minutes	7.1 ± 3.7	11.3 ± 5.9	<0.05
Mean ± SD time to discharge from the PACU	20.0 ± 7.9	26.7 ± 11.2	<0.05
Anaesthetic consumption: mean ± SD end-tidal sevoflurane concentration (%)			
Maintenance of GA	1.8 ± 0.4	2.4 ± 0.	<0.05
Last 15 minutes of GA	1.6 ± 0.6	2.1 ± 0.7	<0.05
End of procedure	1.1 ± 0.6	1.5 ± 0.7	NS
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs			
Opioid use, *n* (%)	37 (92.5)	35 (100)	NR
Other morbidity	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; NS, not statistically significant ($p \geq 0.05$).

Additional results/comments (e.g. early response factors, QoL)

Primary outcome not specified but the main focus appears to be on anaesthetic consumption and recovery times

Stated there were no statistically significant differences among groups for mean arterial pressure or heart rate recorded during surgery (no quantitative data or *p*-values provided)

Stated there were no intergroup differences in any measured variables between group 2 and a historical control group – showing no change in clinical practice during the trial

Methodological comments

Allocation to treatment groups: stated random allocation but sequence generation method not reported

Allocation concealment: NR

Blinding: single observer blinded to the patient groups was responsible for all PACU discharge assessments

Analysis by ITT: unclear: ITT not mentioned and sample sizes not reported for outcomes

Comparability of treatment groups at baseline: stated no statistically significant differences in demographic data between the groups (no *p*-values reported), but data were only provided for age, weight and sex, which were similar in the two study groups. No information was provided on ethnicity or health status

Method of data analysis: non-normally distributed variables (not specified) were identified by Kolmogorov–Smirnov statistic then log-transformed. Parametric data (not specified) were compared between group 1 and group 2 using Bonferroni-corrected *t*-tests. Chi-squared test was used to compare sex distribution

Sample size/power analysis: NR

Attrition/dropout: none reported

General comments

Generalisability: North American paediatric population aged 6–18 years undergoing tonsillectomy and/or adenoidectomy under sevoflurane for GA; socioeconomic details not reported. Not specifically identified as at risk for intraoperative awareness

Intercentre variability: NA (appears to be a single-centre study)

Conflict of interests: funded in part by Aspect Medical Systems (AMS) who supplied the BIS monitor. One author was employed by AMS; another author was a paid consultant to AMS

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given
Allocation concealment	Unclear	No information given
Performance bias		
Blinding of participants and personnel	Unclear	No information given
Detection bias		
Blinding of outcome assessment	Unclear	Single observer blinded to the patient groups was responsible for all PACU discharge assessments. Not reported whether or not observers were blinded for other outcomes
Attrition bias		
Incomplete outcome data	Unclear	Attrition and sample sizes for outcomes not reported
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting
Other bias		
Other sources of bias	High	Notable conflict of interest declared likely to favour results supporting the utility of BIS-guided anaesthesia

Bhardwaj and Yaddanapudi

Reviewer 1: JS	Reviewer 2: JB		
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Bhardwaj and Yaddanapudi[46] **Year:** 2010 **Study design:** RCT **Number of centres:** one **Country:** India **Sponsor:** not stated	**Group 1:** BIS Monitor Model A-2000 IP X 2 (Aspect Medical Systems Inc., Newton, MA, USA) (propofol infusion rate manually altered by 20 µg/kg/minute to achieve a BIS value between 45 and 60) **Group 2:** Standard clinical practice (propofol infusion rate manually altered by 20 µg/kg/minute if systolic blood pressure changed by >20% of baseline) Commencement of monitoring: following transition to the operating theatre and just before start of induction of anaesthesia. Monitoring continued in recovery room and monitored until patients achieved discharge criteria (Steward score of 6) BIS monitoring took place in both groups, but monitor was kept covered in group 2 Length of experience/training of anaesthetist: not stated	**Total numbers involved:** 50; group 1 = 25; group 2 = 25 Premedication used: midazolam 0.5 mg/kg General anaesthetic used: propofol 3 mg/kg (induction). Propofol 150 µg/kg/minute with nitrous oxide in oxygen (FiO_2 0.33) (maintenance) Regional anaesthesia used: none Analgesia used: morphine 0.1 mg/kg (induction). Additional dose of opioid (fentanyl or morphine) was administered if signs of inadequate anaesthesia detected Muscle relaxants used: atracurium (0.5 mg/kg) used to facilitate tracheal intubation Antinausea drugs used: NR Other drugs used: atropine used to treat bradycardia (heart rate <80 of baseline). Neostigmine (0.05 mg/kg and atropine (0.025 mg/kg) used for reversal of neuromuscular blockade Type of surgery: elective urogenital surgery Duration of surgery (minutes), mean (SD): group 1 = 65.6 (29.2); group 2 = 71.8 (27.3) Duration of GA (minutes), mean (SD): group 1 = 88.6 (31.8); group 2 = 95.1 (28.3) **Inclusion criteria:** ASA 1 children aged 2–12 years undergoing elective urogenital surgery of about 1 hour in duration under GA **Exclusion criteria:** Patients with epilepsy and those taking drug known to affect EEG **Baseline measurements:** Sex (male), *n* (%): group 1 = 21/25 (84%); group 2 = 24/25 (96%) Age (years), mean (SD): group 1 = 6.3 (3.2); group 2 = 6 (3) Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 18.7 (8.1); group 2 = 18.5 (5.9) ASA grade: all grade 1 Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** NA **Place of anaesthetic administration:** premedication took place prior to transfer to the operation theatre. GA was initiated in the operation theatre	**Primary outcome:** • Reduction in consumption of propofol **Secondary outcome:** • Recovery from anaesthesia **Length of follow-up:** NA (all outcomes measured at the end of surgery) **Methods of assessing outcomes:** Steward recovery scoring system used to assess eligibility for discharge from the recovery room (eligibility = score of 6) Duration of anaesthesia was defined as the time from the start of propofol bolus for induction to extubation of trachea. Duration of surgery was defined as the time from surgical incision to the application of last suture

NA, not applicable; NR, not reported; SD, standard deviation.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	Time to eye-opening and time to response to commands reported to be comparable in the two groups No difference in the time interval between end of anaesthesia and return of consciousness between the groups on basis of log-rank test; ($p = 0.86$)		
Time to extubation	Time to extubation reported to be comparable in the two groups		
Time to discharge to/from the recovery room	Time to achieve a Steward recovery score of 6 (for discharge from the recovery room) reported to be comparable in the two groups		
Anaesthetic consumption			
Propofol consumption during maintenance of anaesthesia, mean (SD)	108.6 µg/kg/minute (37.8)	106.6 µg/kg/minute (38.9)	NR Mean difference 1.9 (95% CI –19.9 to 23.7)
Total propofol consumption, mean (SD)	232.6 mg (136.7)	250.8 mg (118.2)	NR Mean difference –18.1 (95% CI –68.2 to 76)
Duration of propofol infusion, mean (SD)	82 minutes (29.2)	86 minutes (28.5)	NR Mean difference –4 (95% CI –20 to 13.5)
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs			
Morphine consumption, Mean (SD)	1.9 (08)	1.9 (0.6)	NR Mean difference –0.01 (95% CI –0.4 to 0.4)
Other morbidity, *n/N* (%)			
Hypertension	5/25 (20%)	5/24 (21%)	NR
Hypotension	6/25 (24%)	7/24 (29%)	NR
Bradycardia	8/25 (32%)	6/24 (25%)	NR
Mortality	NR	NR	NR

NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Mean propofol infusion rates at various time intervals during the course of surgery were similar in the two groups

The number of patients requiring additional opioids was similar in both groups (two patients in group 1 compared with three patients in group 2)

Mean heart rate and systolic blood pressure were not statistically different between the groups during the duration of surgery

Methodological comments

Allocation to treatment groups: computer-generated randomisation table

Allocation concealment: randomisation to the two groups was performed by opening a sealed envelope

Blinding: NR

Analysis by ITT: all patients received their allocated intervention. Only one patient was excluded from the analysis (group 2) because the child received lower propofol infusion rate owing to wrong dose calculation. Note that table 1 which provides demographic data and study outcomes lists there being 25 patients in each group

Comparability of treatment groups at baseline: authors state that the two study groups were comparable in terms of demographic variables (age, weight, sex)

Method of data analysis: age, weight, heart rate, systolic blood pressure, and duration of anaesthesia, surgery and propofol infusion were compared between groups using Student's *t*-test, whereas the BIS values were compared between groups using Mann–Whitney *U*-test

Sample size/power analysis: calculated that 22 patients required in each study group to detect a 20% difference in propofol consumption [average requirement of propofol 150 μg/kg/minute (SD 30) with an alpha error of 0.05 and power of 90%]. To compensate for any exclusion 25 patients were studied in each group

Attrition/dropout: as above, one patient was excluded from the analysis from group 2

General comments

Generalisability: authors state that they used the three-sensor device for BIS monitoring and that it does not use the new XP technology. The newer version became available later in the study but was not used as the algorithm in the newer device may be different and may affect results. Results of this study may therefore not be applicable to newer versions of BIS monitors

Intercentre variability: NA

Conflict of interests: reported as 'Nil'

Other: the authors note that the Steward score for anaesthetic recovery has never been formally validated for the paediatric patient population, although is widely accepted as a tool in paediatric anaesthesia research

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Computer-generated randomisation table
Allocation concealment	Unclear	Sealed envelopes were used although it does not say whether or not they were opaque
Performance bias		
Blinding of participants and personnel	Unclear	NR
Detection bias		
Blinding of outcome assessment	Unclear	NR
Attrition bias		
Incomplete outcome data	Low	Only one exclusion from the study
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

NR, not reported.

Reviewer 1: GF	Reviewer 2: JS		
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Chan *et al.*[47] **Year:** 2010 **Study design:** RCT **Number of centres:** two **Country:** China **Sponsor:** none reported Note: abstract only	**Group 1:** BIS (no further details) Target device/index value: 40–60 during maintenance of GA Commencement of monitoring: NR **Group 2:** routine practice Anaesthesia adjusted according to traditional clinical signs and haemodynamic parameters (no further details). BIS was measured but values were not revealed to the anaesthesiologist Length of experience/ training of anaesthetist: NR	**Total numbers involved:** Starting number: 921; group 1, 449; group 2, 452 Number randomised per group not stated. Difference (20 patients) between starting number and sample size reported for outcomes but unclear whether this reflects attrition before or after randomisation NB. There was also a matched control group of 211 non-surgery patients which were outside of the randomised cohort – unclear in the presentation of one outcome whether 'control' refers to this group or to the routine practice group Premedication used: NR General anaesthetic used: not explicitly reported but implied that both an inhalational agent and i.v. propofol were involved Regional anaesthesia used: not reported Analgesia used: NR Muscle relaxants used: NR Antinausea drugs used: NR Other drugs used: NR Type of surgery: stated as major non-cardiac surgery (no other details) Duration of surgery: NR Duration of GA: NR **Inclusion criteria:** elderly patients (>60 years) undergoing major non-cardiac surgery. No other details reported **Exclusion criteria:** none reported **Baseline measurements:** stated that patient characteristics and surgical details were similar between groups. No baseline data reported **Losses to follow-up:** NR **Place of anaesthetic administration:** NR	**Outcomes (not stated whether primary or secondary):** • POCD • BIS device values • Anaesthetic consumption **Length of follow-up:**1 week and 3 months after surgery **Methods of assessing outcomes:** POCD assessed by a battery of eight neuropsychology tests before and at 1 and 3 weeks after surgery (no information on the tests reported). POCD was confirmed when two or more test parameters or the combined *z*-score >1.96 (no further information given)

NR, not reported.

Outcome	Group 1 (BIS) ($n = 449$)	Group 2 (routine care) ($n = 452$)	p-value
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	NR	NR	NR
Time to extubation	NR	NR	NR
Time to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption			
ETAC	25.3% reduction vs group 2[a]	NR	NR
Target plasma propofol concentration	20.7% reduction vs group 2[a]	NR	NR
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction), *n* (%)[b]			
POCD, 1 week post surgery	146 (32.5)	177 (39.1)	0.07
POCD, 3 months post surgery	36 (8.1)	54 (12.0)	0.03 [OR (95% CI) 1.6 (1.0 to 2.4)]
Mortality	NR	NR	NR

NR, not reported.

a Assumed by reviewer that this comparison was between groups 1 and 2; however, the wording of the results does not rule out that the comparison may instead have been between group 1 and the matched 'control' group.

b Percentages only were provided in the abstract; numbers of patients estimated by reviewer.

Additional results/comments (e.g. early response factors, QoL)

Only an abstract is available, hence, the information reported is limited

Reported ETAC and target plasma propofol concentration outcomes which would correspond, respectively, to inhaled and i.v. anaesthesia; unclear how the patients received these different types of anaesthesia, as no subgroups were specified

Methodological comments:

Allocation to treatment groups: random assignment. No further details given

Allocation concealment: NR

Blinding: NR

Analysis by ITT: not discernible as the number randomised and the analysis methods were not reported

Comparability of treatment groups at baseline: stated patient characteristics and surgical details similar between groups, but no data provided for any variables

Method of data analysis: NR

Sample size/power analysis: NR

Attrition/dropout: NR. The starting number of patients (921) is 20 more than the total sample size indicated for outcomes data (449 + 452 = 901); unclear whether or not this difference reflects attrition pre or post randomisation

General comments

Generalisability: elderly Chinese patients (>60 years) undergoing major non-cardiac surgery under GA, but limited information on the types of anaesthesia (appears to include both inhaled and i.v.); unclear population characteristics (sex, weight, comorbidities not reported); unclear surgical procedures (no information reported); and unclear which groups some outcomes were reported for. Not reported whether or not population was at high risk of intraoperative awareness

Intercentre variability: NR

Conflict of interests: none reported

NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given
Allocation concealment	Unclear	No information given
Performance bias		
Blinding of participants and personnel	Unclear	No information given
Detection bias		
Blinding of outcome assessment	Unclear	No information given
Attrition bias		
Incomplete outcome data	Unclear	No information given – number randomised not discernible
Reporting bias		
Selective reporting	Unclear	Stated that postoperative complications were recorded, but these were not reported

Choi *et al.*

Reviewer 1: JS	Reviewer 2: GF		
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Choi *et al.*[54] **Year:** 2010 **Study design:** RCT **Number of centres:** not stated (presume single-centre) **Country:** South Korea **Sponsor:** Dong-A University	**Group 1:** E-Entropy (GE Datex-Ohmeda S/5 Anaesthesia monitor, Helsinki, Finland) Target device/index value: state entropy 40–50 Entropy sensor stripes were applied upon arrival in the operating room **Group 2:** standard practice Sevoflurane adjusted to maintain heart rates and systolic blood pressures within 20% of the baseline values Entropy indices were recorded with the anaesthesiologist blinded to them Length of experience/ training of anaesthetist: not stated	**Total numbers involved:** 80 patients enrolled. 39 were included in each group Premedication used: i.v. midazolam (0.15 mg/kg) General anaesthetic used: 5% vol% sevoflurane in oxygen at fresh gas flow of 5 l/minute (induction). Sevoflurane administration was started at 2.5 vol% in air and oxygen 1.5 l/minute Regional anaesthesia used: not stated Analgesia used: intraoperative analgesics were not used as their sedative effect may not be detected by entropy monitoring. ketorolac (non-steroidal anti-inflammatory) 0.5 mg/kg i.v. administered following sevoflurane cessation Muscle relaxants used: rocuronium 0.6 mg/kg i.v. used for endotracheal intubation Antinausea drugs used: NR Other drugs used: NR Type of surgery: tonsillectomy/adenoidectomy Duration of surgery (minutes), mean (SD): group 1 = 41.4 (± 14.8); group 2 = 48.1 (± 17.8) Duration of GA (minutes), mean (SD): group 1 = 64.3 (± 16.4); group 2 = 67.9 (± 19.7) **Inclusion criteria:** ASA physical status I-II, aged 3–12 years, scheduled for tonsillectomy/ adenoidectomy **Exclusion criteria:** children with any neurological disease or on any antiseizure medication **Baseline measurements:** Sex (male), *n* (%): group 1 = 25/39 (64); group 2 = 27/39 (69) Age (years), median (range): group 1 = 4.0 (3.0–12.0); group 2 = 6.0 (3.0–11.0) Ethnic groups, *n* (%): NR Weight (kg), median (range): group 1 = 24.0 (13.0–35.0); group 2 = 22.0 (14.0–52.0) ASA grade: physical status I–II Risk factors for awareness: none reported Comorbidities: none reported **Losses to follow-up:** NR **Place of anaesthetic administration:** not stated	**Primary outcome:** • Reduction in sevoflurane use, as expressed by end-tidal sevoflurane concentration (described as the 'final end-point') **Secondary outcomes:** • Time to extubation • Time to eye opening • Time to orientation • Time to complete recovery • Intraoperative recall • Haemodynamic parameters (heart rate; systolic and diastolic blood pressure) • Entropy values (state and response entropy) **Length of follow-up:** longest follow-up appears to be the first postoperative day (for intraoperative recall) **Methods of assessing outcomes:** end-tidal sevoflurane concentration, entropy values and heart rate were continuously recorded using the S/5 Collect software program (GE Healthcare) on a computer hard drive for off-line analysis. The average end-tidal sevoflurane concentration, entropy values and haemodynamic parameters during anaesthetic maintenance were calculated using data collected from the application of the gag retractor to the end of surgery Patients were interviewed about intraoperative recall in the PACU and on the first postoperative day by an independent nurse Time to the various recovery parameters was measured following discontinuation of sevoflurane. Complete recovery was defined as a score of 9 or more on a modified Aldrete score

NR, not reported.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall	Anaesthesia and surgery-related memories were not reported by any patients in the postoperative interview		
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia, mean (SD)			
Eye-opening	14.3 (3.6)	18.0 (3.3)	NS
Orientation	18.2 (4.0)	23.3 (5.0)	<0.05
Complete recovery	24.3 (7.3)	28.8 (5.7)	<0.05
Time (minutes) to extubation, mean (SD)	8.3 (1.4)	11.9 (2.5)	<0.05
Time (minutes) to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption, end-tidal sevoflurane%, mean (SD)	2.2 (0.3)	2.6 (0.4)	<0.05
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; NS, not statistically significant.

Additional results/comments (e.g. early response factors, QoL)

Systolic and diastolic blood pressure were significantly higher in group 1 compared with group 2 during anaesthesia maintenance ($p<0.05$)

Methodological comments

Allocation to treatment groups: random, no further information given

Allocation concealment: parents opened a sealed envelope

Blinding: not stated

Analysis by ITT: NR. Analysis excludes two patients out of the 80 enrolled because of 'technical problems'. It is not clear whether this was pre or post randomisation

Comparability of treatment groups at baseline: authors state that there were no statistically significant demographic differences between the groups or in the anaesthetic times or duration of surgery

Method of data analysis: nominal data were compared using the chi-squared test and parametric data were compared using the two-sided *t*-test

Sample size/power analysis: applying a priori analysis, at least 33 patients had to be enrolled in each group to detect a reduction of 20% in end-tidal sevoflurane concentration with an alpha of 0.05 and a statistical power of 0.9. Forty patients were enrolled in each group for redundancy

Attrition/dropout: two patients out of the 80 enrolled were excluded from the analysis because of 'technical problems'

General comments

Generalisability: results applicable to Korean children without any apparent comorbidities undergoing tonsillectomy/adenoidectomy. Not stated to be at increased risk for intraoperative awareness

Intercentre variability: NA (presumed single centre)

Conflict of interests: none reported

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given on randomisation method
Allocation concealment	Unclear	States that parents opened a sealed envelope, although it is not reported whether or not the envelope was opaque
Performance bias		
Blinding of participants and personnel	Unclear	No information given
Detection bias		
Blinding of outcome assessment	Unclear	No information given
Attrition bias		
Incomplete outcome data	Low	Two patients were excluded from the analysis, although it is not clear at when or why these exclusions happened (other than for 'technical problems'). As this is a relatively low number, and given that the study recruited a greater number of participants than were needed (as estimated from the power calculation), attrition bias may be low
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

Reviewer 1: JB **Reviewer 2: JS**

Reference and design	Technology	Participants	Outcome measures
Author: Ellerkmann *et al.*[62] **Year:** 2010 **Study design:** RCT **Number of centres:** 1 **Country:** Germany **Sponsor:** not stated	**Group 1:** Entropy module (GE Healthcare, version not stated) with BIS monitor A-2000 Propofol adjusted State entropy to target value of 50 during maintenance Target state entropy value of 60 to facilitate rapid emergence from anaesthesia (15 minutes before expected end of surgery) **Group 2:** BIS Monitor A-2000 (version XP, software version 4.0) Propofol adjusted to target value of 50 during maintenance Target value of 60 to facilitate rapid emergence from anaesthesia (15 minutes before expected end of surgery) In the E-Entropy and BIS group, a propofol bolus of 0.25 mg/kg could be given in the presence of a sudden increase in state entropy or BIS above the index value of 65 Group 3: standard practice (blood pressure, heart rate, sweating, tear production, movement) Propofol increased in steps of 1 mg/kg/hour as necessary for clinical parameters During maintenance of anaesthesia, all patients assessed for signs of inadequate anaesthesia, hypotension or bradycardia Commencement of monitoring: in operating room Further details unclear In group 3 both BIS and E-Entropy monitors were covered behind a curtain; in the BIS and E-Entropy group, either only the BIS monitor or only the E-Entropy module was uncovered Length of experience/training of anaesthetist: 'experienced anaesthesiologist'	**Total numbers involved:** 90; group 1, 30; group 2, 30; group 3, 30 Premedication used: midazolam 7.5 mg orally on morning of surgery General anaesthetic used: bolus of 2 mg/kg propofol and a continuous propofol infusion of 6 mg/kg/hour. A propofol bolus of 0.5 mg/kg given in the presence of unexpected somatic intraoperative response Regional anaesthesia used: mentioned in abstract but no further details given Analgesia used: remifentanil infusion at 0.4 µg/kg/minute to induce anaesthesia followed 5 minutes later by propofol Muscle relaxants used: 0.1 mg/kg cis-atracurium to allow tracheal intubation after which remifentanil reduced to 0.08 µg/kg/minute in order to tolerate tube Antinausea drugs used: NR Other drugs used: 0.3 ml of i.v. vasopressor (Akrinor, 1 ml contains 100 mg cafedrine and 5 mg theodrenaline to treat hypotension). 0.5 mg atropine (to treat brachycardia) Type of surgery: orthopaedic of upper or lower extremity Duration of surgery: NR Duration of GA (minutes), mean (SD): group 1 = 123.7 (44.6); group 2 = 100.0 (30.7); group 3 = 119.5 (50.6) **Inclusion criteria:** ASA I, II or III adults 18–80 years undergoing minor surgery expected to last at least 1 hour **Exclusion criteria:** history of disabling central nervous or cerebrovascular disease, hypersensitivity to opioids or substance abuse, or treatment with opioids or any psychoactive medication **Baseline measurements:** Sex (male) *n* (%): group 1 = 15/25 (60%); group 2 = 18/27 (67%); group 3 = 15/27 (56%) Age (years), mean (SD): group 1 = 58.1 (14.2); group 2 = 50.6 (15.7); group 3 = 53.6 (18.4)	**Primary outcome:** • Reduction in propofol consumption **Secondary outcome:** • Remifentanil consumption, recovery time, duration of anaesthesia, intraoperative awareness, BIS and E-Entropy values **Length of follow-up:** third postoperative day for awareness **Methods of assessing outcomes:** Method of assessing reduction in propofol consumption not reported End of surgery defined as the final surgical suture Recovery from anaesthesia assessed by measuring time between last suture and spontaneous opening of eyes allowing extubation Aldrete score evaluated at extubation Modified Aldrete score for assessing discharge from PACU Intraoperative awareness by 'standardised interview' (first and third day postoperative days) (Nordström *et al.*[96])

NR, not reported.

Reviewer 1: JB Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 76.4 (16.4); group 2 = 82.4 (15.7); group 3 = 76.7 (14.1) ASA grade, I/II/III: group 1 = 4/15/6; group 2 = 10/16/1; group 3 = 10/10/7 Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** none **Place of anaesthetic administration:** premedication prior to operating theatre; GA initiated in operating theatre	

NR, not reported.

Outcome	Group 1: E-Entropy (*n* = 25)	Group 2: BIS (*n* = 27)	Group 3: SP (*n* = 27)	*p*-value
Intraoperative awareness/recall	0	0	0	
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR	
Time (minutes) to emergence from anaesthesia, mean (SD) NB. Abstract states this is time to extubation	9.2 (3.9)	6.8 (2.9)	7.3 (2.9)	$p = 0.023$ Group 1 vs group 2 NS (no *p-value* given) for group1/2 vs group 3
Time (minutes) to extubation	NR	NR	NR	
Time (minutes) to discharge to/from the recovery room	NR	NR	NR	
Anaesthetic consumption				
Propofol (μg/kg/minute), mean (SD)	106 (24)	104 (20)	101 (22)	$p = 0.27$ Group 1/2 vs group 3
Remifentanil (μg/kg/minute), mean (SD)	0.08 (0.02)	0.08 (0.02)	0.09 (0.02)	$p = 0.56$
Bolus of propofol following rise in BIS or Entropy (state entropy) above 65 or sudden unexpected somatic response, *n*	12	8	10	
HRQoL	NR	NR	NR	
Nausea/vomiting/antisickness drugs	NR	NR	NR	
Pain/pain-relieving drugs	NR	NR	NR	
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR	
Mortality	NR	NR	NR	

NR, not reported, SP, standard practice.

Additional results/comments

Aldrete scores (10/10) at extubation were group 1 = 8.4 (SD 0.6), group 2 = 8.6 (SD 0.5), group 3 = 8.8 (SD 0.4); group 1 vs group 3 $p = 0.045$

Aldrete scores similar 1 minute after extubation

Various E-Entropy and BIS values reported for all three groups; differences between groups not significant

Methodological comments

Allocation to treatment groups: randomised by drawing lots from a closed box

Allocation concealment: NR

Blinding: NR

Analysis by ITT: no

Comparability of treatment groups at baseline: no differences between groups in age, weight and height by analysis of variance; not reported for sex and ASA status

Method of data analysis: normally distributed data compared with between-group analysis of variance and Tukey's HSD (honestly significant difference) post hoc test if global analysis of variance result was significant; a covariance analysis of variance was performed for 'recovery time' and the covariate 'duration of anaesthesia'. Data not normally distributed compared using Kruskal-Wallis analysis

Sample size/power analysis: calculated that at least 25 patients had to be investigated in each group to detect a reduction of 20% in propofol consumption with a standard deviation of 20% in propofol consumption in each group with a type I error of 0.05 and a statistical power of 0.86

Attrition/dropout: patients excluded from analysis because of insufficient regional anaesthesia or EEG data loss were group 1 = 5, group 2 = 3, group 3 = 3

General comments

Generalisability: to separate hypnotic and analgesic components of anaesthesia, all patients received regional anaesthesia catheters for intra- and postoperative pain control prior to investigation (i.e. pain perception completely blocked), which could limit generalisability. Also more than one type of surgery was included and more than one regional anaesthesia technique that might contribute to different levels of analgesia. Authors state that similar results may not have been obtained with less experienced anaesthetists. Results applicable to adult patients receiving i.v. GA (and regional anaesthesia) assumed not to have significant morbidities

Intercentre variability: NA

Conflict of interests: NR

NA, not applicable; NR, not reported.

Domain	Reviewer's judgement (state: low/high/unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Drawing lots
Allocation concealment	Unclear	No details reported
Performance bias		
Blinding of participants and personnel	Unclear	Monitors covered as appropriate
Detection bias		
Blinding of outcome assessment	Unclear	No details
Attrition bias		
Incomplete outcome data	High	Group 1, 17% patients excluded from analysis; group 2 and group 3, 10%. Not balanced between groups, although reasons similar across groups
Reporting bias		
Selective reporting	Low	No evidence of selective reporting
Other bias		
Other sources of bias		

Reviewer 1: GF Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Gruenewald *et al.*[55] **Year:** 2007 **Study design:** RCT **Number of centres:** 1 (not explicitly stated) **Country:** Germany **Sponsor:** GE Healthcare supplied the M-Entropy module and electrodes	**Group 1:** E-Entropy + standard practice S/5™ M-Entropy module (GE Healthcare); BIS XP monitor (Aspect Medical Systems Inc.); anaesthetist viewed only the entropy monitor Target device/index value: 40–60 for state entropy (>60 acceptable in final 15 minutes of surgery); <10 for response-state entropy difference Commencement of monitoring: prior to induction of anaesthesia, after arrival in the operating theatre **Group 2:** standard practice only Dosage adjustments of anaesthesia at the discretion of the anaesthetist based on standard clinical signs (hypertension (blood pressure >120% of baseline), hypotension (blood pressure<80% of baseline), tachycardia (>90 beats/minute), bradycardia (heart rate <80% of baseline), somatic arousal (coughing, chewing, grimacing), somatic response (purposeful movement) Also monitored by same entropy and BIS devices as group 1, but the monitor screen was covered to obscure the processed EEG parameters Both groups: anaesthesia was guided to achieve rapid recovery Length of experience/training of anaesthetist: stated only that anaesthesia was supervised by an experienced staff anaesthetist	**Total numbers involved:** 72; group 1, 37; group 2, 35 Premedication used: oral benzodiazepine (dipotassium chlorazepate) 20 mg; midazolam 7.5 mg General anaesthetic used: Induction: Propofol 2 mg/kg; remifentanil 0.3–0.5 μg/kg/minute Maintenance: propofol and remifentanil (dose adjusted according to entropy or clinical signs) Regional anaesthesia used: none reported Analgesia used: piritramide 0.1 mg/kg 15 minutes before end of surgery Muscle relaxants used: rocuronium 0.6 mg/kg Antinausea drugs used: none reported Other drugs used: hypotension and bradycardia were managed where appropriate with unspecified pharmacologic agents (dose not reported) Type of surgery: routine elective gynaecological laparoscopy Duration of surgery: ≥1 hour Duration of GA, minute, mean ± SD: group 1, 110 ± 39; group 2, 111 ± 46 **Inclusion criteria:** NR (implied adult female population) **Exclusion criteria:** pregnancy, neurological or neuromuscular disease, use of CNS-active medication, abuse of alcohol or illicit drugs **Baseline measurements:** Sex (male) *n* (%): 0 (0) Age (years) mean ± SD: group 1, 38 ± 9; group 2, 33 ± 9 Ethnic groups, *n* (%): NR Weight (kg) mean ± SD: group 1, 68 ± 15; group 2, 68 ± 13 ASA grade 1/2, *n*: group 1, 14/23; group 2, 11/24 Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** NR **Place of anaesthetic administration:** NR	**Primary outcomes:** • Recovery time (from discontinuation of propofol and remifentanil to eye-opening) **Secondary outcomes:** • Intraoperative awareness • Pain, nausea, vomiting • Anaesthetic consumption • Device values (BIS, state entropy, response entropy, state-response entropy difference); • Haemodynamic variables • Somatic responses (purposeful movement) • Cumulative probability of emergence • Patient satisfaction **Length of follow-up:** on arrival in the recovery room (Observer Assessment of Alertness and Sedation scale, nausea and vomiting, and pain questionnaires), and 24 hours post surgery (memory or awareness and satisfaction) **Methods of assessing outcomes:** Intraoperative awareness: Questions about memory or awareness during the ward, induction room, surgery, extubation or recovery room stages Postoperative pain rating: 0–10 scale PONV: assessed by unspecified questions Patient satisfaction: 0–100 scale (100 = totally satisfied) Awareness and satisfaction outcomes assessed by patient interview by an anaesthesiologist blinded to the treatment groups Method of assessing anaesthetic consumption not reported

NR, not reported.

Outcome	Group 1 (entropy + standard practice)	Group 2 (standard practice only)	*p*-value
Intraoperative awareness/recall			
Patients reporting awareness during the procedure when assessed at 24 hours post surgery, *n* (%)	0 (0)	1 (2.8)[a]	NR
Stated no difference between groups in awareness or explicit memory assessed 24 hours post surgery (no further quantitative data provided)			
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia			
Median [interquartile] (range) time to eye-opening	3 [1–5] (0–9)	4 [3–6] (0–14)	NS
Time (minutes) to extubation	NR	NR	NR
Time (minutes) to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption (induction + maintenance; µg/kg/minute), mean (SD)			
Propofol	81 ± 22	95 ± 14	<0.01
Remifentanil	0.46 ± 0.08	0.39 ± 0.08	<0.001
HRQoL	NR	NR	NR
Nausea/vomiting			
Nausea and vomiting, *n* (%) (on arrival in recovery room)	15 (41)	13 (37)	NS
Antisickness drugs: none reported			
Pain			
Median [interquartile] (range) pain intensity score (on arrival in recovery room)	6 [4–7] (2–10)	4 [3–5] (1–10)[b]	0.03
Pain-relieving drugs			
Stated analgesia (piritramide) did not differ between groups (no quantitative data reported)			
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; NS, not statistically significant ($p \geq 0.05$).

a Implied this was a female patient who did not report feeling any pain.

b As reported with the original data: meaning not stated.

Additional results/comments (e.g. early response factors, QoL)

Patients in group 2 had significantly more hypertension, hypotension, tachycardia, bradycardia and somatic responses (purposeful movements) compared with those in group 1 (47 vs 27 total events, respectively; $p<0.01$). However, the incidence of purposeful movement alone (15 vs 18 total events respectively) did not differ significantly ($p\geq0.05$) between group 2 and group 1

In addition to the emergence data above, cumulative probability of non-emergence was reported in a Kaplan–Meier survival analysis graph (data not extracted)

Median [interquartile] (range) patient satisfaction score 24 hours post surgery: group 1: 93 [80–100] (50–100); group 2: 90 [80–100] (50–100); difference not statistically significant ($p\geq0.05$)

Three patients in group 2 and one patient in group 1 had EEG-derived variables that were considered out of range after skin incision (no further explanation provided)

Methodological comments

Allocation to treatment groups: randomisation to group 1 or group 2 was done by opening a sealed envelope. Sequence generation method and nature of the envelope contents not reported

Allocation concealment: sealed envelope used, not stated whether or not opaque

Blinding: Observer Assessment of Alertness and Sedation Scale, PONV, pain, and recall questions were completed by patient interview by an anaesthesiologist who was blinded to the treatment groups. Postoperative care was supervised by a recovery room nurse blinded to treatment groups. However, stated that entropy and standard practice guidance could not be performed in a blinded fashion

Analysis by ITT: stated that all patients were included into the final analysis

Comparability of treatment groups at baseline: patients in group 1 had mean age 5 years older than group 2; group 1 had a slightly higher ratio of ASA class 1 to class 2 (i.e. slightly less severe illness rating) than group 2. Height (not extracted) and weight were similar in the two groups. Ethnicity not reported. Stated that there were no significant differences in patients' characteristics (*p*-values not reported)

Method of data analysis: t-tests for normally distributed data; Mann–Whitney *U*-tests for non-normally distributed data; repeated measures analysis of variance 'as appropriate' (no further details given). Distribution of emergence times by study group compared using Kaplan–Meier log-rank survival analysis (calculating the cumulative probability of patients remaining unconscious after discontinuation of the anaesthetic drugs)

Sample size/power analysis: sample size of 34 based on a previous study by Kreuer *et al.*,[63] assuming a difference in emergence (eye-opening) of 3 minutes, an error of 0.05 and 90% power. Study was powered for time to eye-opening; stated that there were too few subjects to show a significant effect on intraoperative awareness, given the low incidence rate

Attrition/dropout: NR

General comments

Generalisability: women-only study, mid-30s age group, with ASA score <3. Population does not appear to be at high risk of intraoperative awareness

Intercentre variability: NA; appears to be a single centre

Conflict of interests: none explicitly reported, but the M-Entropy module and electrodes were provided by the module manufacturer

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given
Allocation concealment	Unclear	Sealed envelopes, not stated whether or not opaque and sequentially numbered
Performance bias		
Blinding of participants and personnel	Unclear	Group 2 anaesthesiologists were blinded to entropy values but group 1 anaesthesiologists were not blinded to clinical practice guidelines; authors stated that entropy and standard practice guidance could not be performed in a blinded fashion, so bias cannot be totally excluded (relevant to performance bias as unclear how much of group 2 intervention was also received by group 1 patients)
Detection bias		
Blinding of outcome assessment	Unclear	Anaesthesiologist who interviewed patients for awareness and satisfaction was blinded to the treatment groups; not reported whether or not assessors of recovery time and anaesthesia consumption were blinded
Attrition bias		
Incomplete outcome data	Unclear	Attrition not reported
Reporting bias		
Selective reporting	Low	All outcomes mentioned in the methods section were reported in the results

Kamal

Reviewer 1: JB Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Kamal *et al*.[48] **Year:** 2009 **Study design:** RCT **Number of centres:** 1 **Country:** Egypt **Sponsor:** not stated	**Group 1:** BIS plug-in modules connected to monitor model A-2000 (Aspect medical Systems, Newton, MA, USA). Software program Datex-Ohmeda S/5 Collect (v4.0) Target BIS index: 50–60. If patient exhibited hypertension or tachycardia treatment depended on BIS value – if BIS >60 then sevoflurane was increased If BIS in target range fentanyl 25–50 µg i.v. given; if BIS <50 sevoflurane decreased and patient checked for lack of analgesia If lack of analgesia fentanyl 25–50 µg i.v. given; if no lack of analgesia labetalol 5–10 mg i.v. given at end of surgery BIS 55–70 to facilitate recovery **Group 2:** standard clinical practice and such that provides early recovery If patient showed hypertension (mean arterial blood pressure >25% above baseline) and tachycardia (heart rate >90 beats/minute) anaesthesia was deepened by increasing inspired sevoflurane or adjusting fentanyl 25–50 µg i.v. or labetalol 5–10 mg i.v. according to anaesthesiologist's discretion Commencement of monitoring: all patients monitored; place and time not explicitly stated In group 2 the monitor display was customised to make BIS values invisible to the attending anaesthesiologist Length of experience/ training of anaesthetist: not stated	**Total numbers involved:** 60; group 1 = 30; group 2 = 30 Premedication used: none used General anaesthetic used: Propofol 1–2 mg/kg i.v. and fentanyl 2–3 µg/kg i.v. (induction) Sevoflurane and 50% nitrous oxide with oxygen 2 l/ minute (continued) Nitrous oxide discontinued, sevoflurane adjusted for BIS index in group 1 and as usual practice in group 2 (10 minutes before last stitch) Sevoflurane discontinued (end of skin closure, beginning of recovery period) Regional anaesthesia used: none used Analgesia used: not stated Muscle relaxants used: atracurium 0.5 mg/kg i.v. Intermittent boluses of atracurium 0.2–0.3 mg/kg i.v. Antinausea drugs used: NR Other drugs used: ephedrine 3–6 mg i.v. or phenylephrine 20–100 µg i.v. (for hypotension). Atropine 0.02 mg/kg i.v. (for bradycardia). Glycopyrate 0.01 mg/kg and neostigmine 0.05 mg/kg i.v. 5 minutes before discontinuation of anaesthesia (to reverse residual neuromuscular blockade) Type of surgery: elective moderate abdominal surgery Duration of surgery (minutes), mean (SD): group 1 = 91.7 (11.3); group 2 = 85.8 (17.4) Duration of GA (minutes), mean (SD): group 1 = 111.7 (14.6); group 2 = 108.7 (10.5) **Inclusion criteria:** ASA I, II, III adults 45-60 years undergoing surgery with expected durations of at least 2 hours **Exclusion criteria:** history of any disabling central nervous or cerebrovascular disease, hypersensitivity to opioids, substance abuse, treatment with opioids or any psychoactive medication and a BMI >40 kg/m^2 **Baseline measurements:** Sex (male), *n* (%): group 1 = 18 (62%); group 2 = 20 (71%) Age (years), mean (SD): group 1 = 51.6 (7.4); group 2 = 52.1 (5.2) Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 87.6 (8.2); group 2 = 91.4 (6.5) ASA grade: not reported by group Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** none **Place of anaesthetic administration:** NR	**Primary outcomes:** • Not specified **Secondary outcomes:** • Not specified **Outcomes:** • Recovery times (awakening, tracheal extubation, orientation, arrival at PACU, discharge from PACU) • BIS index values • Anaesthetic drug consumption **Length of follow-up:** third postoperative day for awareness **Methods of assessing outcomes:** Sevoflurane used calculated using Dion's formula Recovery starting point was immediately after last surgical stitch Aldrete score for assessment of discharge from PACU (>9), at 15-minute intervals by research assistant blinded to group assignment Awakening defined as eye-opening Orientation to place, person and time For intraoperative awareness patients visited on first, second and third day postoperatively and questioned for recall of events, hearing vague sounds, feeling surgical instruments or dressing application, or dreaming

NR, not reported.

Outcome	Group 1 ($n = 29$)	Group 2 ($n = 28$)	p-value
Intraoperative awareness/recall	0	0	
Patient distress and sequelae resulting from perioperative awareness	NR	NR	
Time (minutes) to emergence from anaesthesia after termination of anaesthesia (awakening eye-opening)	4.1 (1.6)	4.4 (1.9)	NS
Time (minutes) to extubation	4.3 (2.1)	4.8 (2.3)	NS
Time (minutes) to discharge to/from the recovery room			
Arrival at PACU	9.4 (1.9)	14.1 (2.8)	$p<0.01$
PACU discharge (minutes)	53.9 (14.7)	78.6 (21.5)	$p<0.01$
Anaesthetic consumption			
Sevoflurane (ml), mean (SD)	5.7 (1.9)	8.4 (2.3)	$p<0.01$
End-tidal sevoflurane (vol%), mean (SD)	0.43 (0.3)	0.59 (0.1)	$p\leq0.01$
Propofol (mg), mean (SD)	161.7 (27.5)	157.9 (35.8)	NS
Fentanyl (μg), mean (SD)	383.7 (62.6)	389.4 (41.5)	NS
HRQoL	NR	NR	
Nausea/vomiting/antisickness drugs	NR	NR	
Pain/pain-relieving drugs	NR	NR	
Other morbidity (e.g. cognitive dysfunction)	NR	NR	
Mortality	NR	NR	

NR, not reported; NS, not statistically significant..

Additional results/comments (e.g. early response factors, QoL)

Orientation (minutes) group 1 = 7.4 (1.5), group 2 = 11.2 (1.9), $p<0.01$

Average BIS index values were statistically significantly lower in group 2 than group 1 during surgery and during anaesthesia (both $p<0.01$)

Patient disorientation (%) after discontinuation of inhalational anaesthetic agents was statistically significantly higher at 15 and 20 minutes postoperatively in group 2 than group 1 ($p<0.01$)

Methodological comments

Allocation to treatment groups: randomised (no details reported)

Allocation concealment: no details reported

Blinding: anaesthetists in the control group (group 2) were blinded to the BIS values. No other blinding reported

Analysis by ITT: no, as three patients not included in analysis

Comparability of treatment groups at baseline: authors state groups comparable but no *p-value*s reported (although results suggest groups are comparable)

Method of data analysis: comparison between groups performed using Mann–Whitney *U*-test. Categorical data were compared using chi-squared test

Sample size/power analysis: NR

Attrition/dropout: as above. One patient in group 1 was desaturated intraoperatively necessitating discontinuation of nitrous oxide, and two in group 2 received excessive fentanyl near the end of surgery

General comments

Generalisability: authors state that anaesthetists vary in the way and timing of reducing anaesthetic drug administration towards the end of surgery and this could have an effect on results (i.e. starting point of recovery process variable). Results applicable to adults receiving inhaled anaesthesia for moderate abdominal surgery

Intercentre variability: NA

Conflict of interests: NR

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No method reported
Allocation concealment	Unclear	No method reported
Performance bias		
Blinding of participants and personnel	Unclear	Reported that anaesthetists for control group were blinded to BIS values
Detection bias		
Blinding of outcome assessment	Unclear	Only reported that research assistant collecting Aldrete score was blinded
Attrition bias		
Incomplete outcome data	Low	Only three patients not included in analysis (see above)
Reporting bias		
Selective reporting	Low	No evidence of selective reporting
Other bias		
Other sources of bias		

Reviewer 1: GF	Reviewer 2: JS		
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Kerssens *et al.*[49] **Year:** 2009 **Study design:** RCT **Number of centres:** NR **Country:** USA **Sponsor:** lead author received an educational grant in support of her salary from Aspect Medical Systems Inc.; one co-author was a paid consultant to Aspect Medical Systems Inc.; stated that Aspect Medical Systems did not financially support the study	**Group 1:** BIS, BIS monitor (XP, algorithm 3.4; Aspect Medical Systems Inc.) Target device/ index value: 50–60 Commencement of monitoring: NR **Group 2:** standard practice Standard clinical signs such as heart rate and blood pressure-guided anaesthesia BIS was recorded but not available to the attending clinician for drug dosing Length of experience/ training of anaesthetist: NR	**Total numbers involved:** 128 Number randomised: group 1, 67; group 2, 61 Premedication used: stated benzodiazepines were not given to any patients pre- or intraoperatively General anaesthetic used: Induction: propofol 2 mg/kg Maintenance: sevoflurane in oxygen using standard ventilation parameters (not specified) Regional anaesthesia used: used only for postoperative pain management Analgesia used: fentanyl 3 μg/kg (induction); 50–100 μg (maintenance) Muscle relaxants used: vecuronium bromide 0.1 mg/kg with additional doses as necessary (tracheal intubation) Antinausea drugs used: none reported Other drugs used: esmolol 0.5 mg/kg for hypertension and phenylephrine 100 μg for hypotension as needed Type of surgery: major orthopaedic surgery (hip or knee replacement) Duration of surgery: NR Duration of GA, minutes, mean ± SD: group 1, 126 ± 51; group 2, 112 ± 48 **Inclusion criteria:** patients aged ≥ 18 years scheduled for hip or knee replacement surgery, primary or revision, under GA **Exclusion criteria:** medical history or status that could compromise or skew EEG recordings; history of illicit drug use; antipsychotic medication treatment; head trauma resulting in the loss of consciousness; CNS disorders (e.g. epilepsy); persons scoring < 24 on the preoperatively administered MMSE (reference cited); severe visual or auditory handicaps; non-fluent-English speakers Baseline measurements (only reported for subset of patients assessed after attrition: group 1, $n = 62$; group 2, $n = 47$, but stated that characteristics of the full sample were similar)	**Main outcomes:** • Word recognition memory (implicit recall) • Recall assessment (explicit recall) **Secondary outcomes:** • Anaesthetic consumption • BIS device values **Length of follow-up:** 6 hours post surgery **Methods of assessing outcomes:** physiological parameters, BIS, end-tidal gas concentrations (every 5 seconds) and vital signs (every 3 seconds) were automatically recorded to a computer using Rugloop (Demed, Belgium) Recall assessment: 6 hours after surgery, consisting of five questions (listed in the paper, similar to Brice interview questions), with additional questions asked as necessary Recognition memory test: conducted after recall assessment. An auditory test in which sequences of predetermined neutral words was played to patients through headphones (rationale of the word selection and language characteristics reported). Word presentation typically started 15 minutes after induction and lasted approximately 42 minutes. The memory test involved playing predetermined combinations of words that had been used during anaesthesia, and distractor words, to patients though headphones. Patients were instructed to listen to each test sequence and select the word played during surgery, or to guess if necessary (three-alternative forced choice)

NR, not reported.

Reviewer 1: GF	Reviewer 2: JS		
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Sex (male), *n* (%): group 1, 28 (45); group 2, 16 (34) Age (years) mean ± SD: group 1, 61.2 ± 11.4; group 2, 63.9 ± 11.8 Ethnic groups, *n* (%): NR Weight (kg) mean ± SD: group 1, 87.9 ± 18.9; group 2: 84.4 ± 14.8 BMI (kg/m^2), mean ± SD: group 1, 30.2 ± 5.6; group 2, 28.9 ± 3.7 ASA grade: ASA I-II: about 50%; ASA III: 50%; stated no differences between groups Baseline data were also reported for MMSE and STAI scores (values were similar in both study groups) Risk factors for awareness: not explicitly reported but population undergoing major orthopaedic surgery and appears to have BMI around 30 kg/m^2 Comorbidities: none reported (patients with comorbidities were excluded) **Losses to follow-up:** attrition reported, with reasons, both pre and post randomisation **Place of anaesthetic administration:** NR	

NR, not reported. STAI, State–Trait Anxiety Inventory.

Outcome	Group 1: BIS ($n = 67$)	Group 2: Standard practice ($n = 61$)	p-value
Intraoperative awareness/recall			
Recall of time period between falling asleep and waking up from anaesthesia, *n* (%)	2 (3.0)	1 (1.6)	Not tested (outcome not powered)
Memory recall: probability of postoperatively selecting a word presented during anaesthesia (target) or not presented during anaesthesia (distractor), mean ± SD			
Target	0.371 ± 0.132	0.323 ± 0.132	NR[a]
Distractor	0.315 ± 0.117	0.338 ± 0.119	NR[a]
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	NR	NR	NR
Time to extubation	NR	NR	NR
Time to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption, end-tidal gas concentration (%) mean ± SD			
Maintenance phase	1.31 ± 0.29[b]	1.56 ± 0.29[c]	< 0.001
During word presentation	1.30 ± 0.31[b]	1.60 ± 0.37[c]	NS[d]
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs – fentanyl analgesia			
Preoperative (μg/kg), mean ± SD	0.27 ± 0.43[b]	0.40 ± 0.47[c]	NS[d]
Intraoperative (μg/kg/hour), including induction dose	2.83 ± 1.04[b]	2.70 ± 1.18[c]	NS[d]
Postoperative (μg/kg)	0.47 ± 0.66[b]	0.55 ± 1.10[c]	NS[d]
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; NS, not statistically significant.

a See additional comments for interpretation of within-group differences.

b Reported for post-attrition subgroup ($n = 62$).

c Reported for post-attrition subgroup ($n = 47$).

d Authors only reported p-values that were considered significant ($p < 0.05$); reviewers have assumed that comparisons reported without p-values were not significant (i.e. $p \geq 0.05$).

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Random assignment using a computer-generated list
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Unclear	BIS was recorded in group 2 but not available to the attending clinician for drug dosing, but unclear whether or not anaesthetist was still aware of group assignment
Detection bias		
Blinding of outcome assessment	Low	Outcome assessors (two of the study authors) were blinded to study group allocation. Note that the method of blinding was not stated; hence, the likelihood of blinding being broken cannot be assessed
Attrition bias		
Incomplete outcome data	Unclear	Attrition with reasons was reported, but not separately by study group
Reporting bias		
Selective reporting	Unclear	STAI scores were reported only for baseline; stated that postoperative STAI score results can be found elsewhere, together with results of a depression questionnaire, but no references were provided

STAI, State–Trait Anxiety Inventory.

Reviewer 1: JB Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Kreuer *et al.*[64] **Year:** 2005 **Study design:** RCT **Number of centres:** one **Country:** Germany **Sponsor:** solely supported by departmental funding	**Group 1:** BIS A-2000 monitor (version XP) Desflurane maintenance anaesthesia adjusted to target value of 50 BIS 15 minutes before expected end of surgery desflurane adjusted to target value of BIS 60 **Group 2:** Narcotrend monitor (software version 2.0 AF). Desflurane maintenance anaesthesia adjusted to target value of D_0 15 minutes before expected end of surgery desflurane adjusted to target value of C_1 In groups 1 and 2: if anaesthesia judged inadequate, although target value achieved, infusion rate of remifentanil increased by 0.05 µg/kg/minute **Group 3:** standard anaesthetic practice protocol If anaesthesia inadequate desflurane concentration increased in steps of 0.5% volume as necessary. If insufficient remifentanil increased by 0.05 µg/kg/minute Hypotension treated with desflurane concentration reduced in steps of 0.5 vol%. Desflurane reduced 15 minutes before end of surgery as much as judged clinically possible without intraoperative awakening Inadequate anaesthesia in all patients defined as hypertension, tachycardia or patient movement, eye-opening, swallowing, grimacing, lacrimation or sweating Commencement of monitoring: in operating theatre Both monitors covered behind curtain for group 3 and invisible to anaesthesiologist; in groups 1 and 2 either only the Narcotrend or only the BIS monitor was uncovered Length of experience/training of anaesthetist: one experienced anaesthesiologist	**Total numbers involved:** 120; group 1 = 40; group 2 = 40; group 3 = 40 Premedication used: midazolam 7.5 mg orally in the evening and on the morning before surgery General anaesthetic used: Induction: remifentanil infusion 0.4 µg/kg/minute, 5 minutes later 2 mg/kg propofol for hypnosis After intubation remifentanil reduced to constant rate of 0.2 µg/kg/minute Desflurane adjusted according to EEG target values or clinical variable 15 minutes before expected end of surgery desflurane reduced in all groups to facilitate rapid emergence from anaesthesia; remifentanil infusion rate remained unchanged throughout end of surgery Regional anaesthesia used: NR Analgesia used: 100 ml infusion of 0.9% NaCl + metamizol 25 mg/kg for postoperative pain relief Muscle relaxants used: 0.5 mg/kg atracurium Antinausea drugs used: NR Other drugs used: hypotension treated with an i.v. vasopressor (Akrinor, 1 ml contains 100 mg of cafedrine and 5 mg of theodrenaline) given at dose chosen by investigator. Atropine 0.5 mg for bradycardia Type of surgery: minor orthopaedic surgery Duration of surgery: NR Duration of GA (minutes), mean (SD): group 1 = 113 (57); group 2 = 122 (50); group 3 = 125 (51) (reported in table 1, although text states this is duration of surgery) **Inclusion criteria:** ASA I, II, III adults 18–80 years scheduled for minor orthopaedic surgery expected to last at least 1 hour **Exclusion criteria:** history of disabling central nervous or cerebrovascular disease, hypersensitivity to opioids or substance abuse, or a treatment with opioids or any psychoactive medication **Baseline measurements:** Sex (male), *n* (%): group 1 = 20/40 (50); group 2 = 20/40 (50); group 3 = 20/40 (50) Age (years), mean (range): group 1 = 46.5 (14.1); group 2 = 44.7 (15.6); group 3 = 43.6 (16.0)	**Primary outcome:** • Time taken to spontaneous opening of eyes **Secondary outcome:** • Not explicitly stated (times to tracheal extubation and arrival at PACU, consumption of desflurane) **Length of follow-up:** third day postoperative for recall **Methods of assessing outcomes:** end of surgery defined as final surgical suture when anaesthesia was stopped Emergence from anaesthesia assessed by measuring times to spontaneous opening of eyes, tracheal extubation and arrival at PACU Desflurane vaporiser weighed before and after anaesthesia to calculate consumption Intraoperative recall assessed by interview in PACU and on first and third postoperative days

Reviewer 1: JB Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 79.3 (16.2); group 2 = 83.6 (18.3); group 3 = 79.0 (17.4) ASA grade, *n*, I/II/III: group 1 = 7/30/3; group 2 = 13/23/4 group 3 = 11/27/2 Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** NR **Place of anaesthetic administration:** in the operating room	

NR, not reported.

Outcome	Group 1 BIS	Group 2 Narcotrend	Group 3 Standard care	*p*-value
Intraoperative awareness/recall	0	0	0	
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR	
Time (minutes) to eye opening, mean (SD)	4.2 (2.1)	3.7 (2.0)	4.7 (2.2)	NS
Reduction compared with standard practice (%)	–10.6	–21.3	NA	
Time (minutes) to extubation, mean (SD)	4.4 (2.2)	3.6 (2.0)*	5.0 (2.4)	*$p<0.05$ Group 2 vs group 3
Reduction compared with standard practice (%)	–12.0	–28.0	NA	
Time (minutes) to discharge to PACU (minutes), mean (SD)	8.4 (2.4)*	8.0 (1.9)*	9.4 (2.4)	*$p<0.05$ Group 1 and 2 vs group 3
Reduction compared with standard practice (%)	–10.6	–15.0	NA	
Anaesthetic consumption per patient				
Desflurane mg, mean (SD)	4861.7 (2948.3)	4655.9 (2891.7)	5547.3 (2396.4)	NS
Reduction compared with standard practice (%)	–12.4	–16.1	NA	
Desflurane mg/minute, mean (SD)	416.2 (99.1)*	374.6 (124.2)*	443.6 (71.2)	*$p<0.05$
Reduction compared with standard practice (%)	–6.2	–15.7	NA	
Normalised remifentanil infusion rates (µg/kg/minute), mean (SD)	0.22 (0.05)	0.22 (0.06)	0.23 (0.07)	NS
HRQoL	NR	NR	NR	
Nausea/vomiting/antisickness drugs	NR	NR	NR	
Pain/pain-relieving drugs	NR	NR	NR	
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR	
Mortality	NR	NR	NR	

NA, not applicable; NR, not reported; NS, not statistically significant.
The asterisks refer to a statistical significance of 0.05.

Additional results/comments (e.g. early response factors, QoL)

End-tidal desflurane concentration reported to be significantly smaller with BIS and Narcotrend compared with standard practice (graph only)

Mean arterial blood pressure at various times points during anaesthesia similar between groups

Vasopressor was necessary in 19 BIS patients, in 19 Narcotrend patients and in 17 standard practice patients

Five patients in each group needed 0.5 mg atropine for treatment of bradycardia

Mean BIS values in the Narcotrend group were higher than those in the BIS group and standard care group (but not statistically significantly so at all time points)

Methodological comments

Allocation to treatment groups: randomised by drawing lots from a closed box

Allocation concealment: no details reported

Blinding: for standard practice group attending anaesthesiologist blinded to EEG readings; in EEG groups either only BIS or only Narcotrend monitor uncovered. Recovery times recorded by blinded investigator. No details reported for desflurane consumption or interview for intraoperative recall

Analysis by ITT: yes

Comparability of treatment groups at baseline: groups reported to be similar at baseline (no statistically significant differences reported)

Method of data analysis: chi-squared test or one-way analysis of variance with Student-Newman-Keuls test for multiple comparisons as appropriate; all tests two-tailed with statistical significance defined as $p<0.05$. Recovery time to opening of eyes also compared using Kaplan–Meier survival analysis

Sample size/power analysis: 35 patients had to be enrolled in each treatment group to provide 80% power to detect a difference of 1.5 minutes at an $\alpha = 0.05$

Attrition/dropout: none

General comments

Generalisability: observed differences were minimal and not clinically significant. Results applicable to patients receiving GA with desflurane-remifentanil for minor orthopaedic surgery

Intercentre variability: NA

Conflict of interests: funding source stated but no other details reported

NA, not applicable.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Drawing lots
Allocation concealment	Unclear	Method not reported
Performance bias		
Blinding of participants and personnel	Unclear	Not all details reported
Detection bias		
Blinding of outcome assessment	Low	Recovery times recorded by blinded investigator. No details reported for other outcomes
Attrition bias		
Incomplete outcome data	Low	ITT analysis
Reporting bias		
Selective reporting	Low	No evidence of selective reporting
Other bias		
Other sources of bias		

Reviewer 1: JB Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Kreuer *et al.*[63] **Year:** 2003 **Study design:** RCT **Number of centres:** one **Country:** Germany **Sponsor:** support solely from departmental sources	**Group 1:** BIS A-2000 monitor (software version 3.0) Propofol TCI continuously adjusted to target value of 50 BIS 15 minutes before end of surgery propofol TCI adjusted to target value of BIS 60 **Group 2:** Narcotrend monitor (software version 2.0 AF) Propofol TCI continuously adjusted to target value of D_0 15 minutes before end of surgery propofol TCI adjusted to target value of C_1 Group 3: standard anaesthetic practice protocol During maintenance all patients were assessed for signs of inadequate anaesthesia (hypertension, tachycardia, movement, eye opening, swallowing, grimacing, lacrimation or sweating), hypotension or bradycardia If anaesthesia inadequate, propofol concentration increased in steps of 0.5 µg/ml as necessary. If insufficient remifentanil increased by 0.05 µg/kg/minute Hypotension treated with propofol concentration reduced in steps of 0.5 µg/ml Propofol reduced 15 minutes before end of surgery as much as judged clinically possible without intraoperative awakening Commencement of monitoring: in operating theatre Both monitors covered behind curtain for group 3 and invisible to anaesthesiologist; in groups 1 and 2 either only the Narcotrend or only the BIS monitor was uncovered Length of experience/ training of anaesthetist: one anaesthesiologist experienced in BIS and Narcotrend monitoring	**Total numbers involved:** 120; group 1 = 40; group 2 = 40; group 3 = 40 Premedication used: 0.15 mg/kg diazepam orally in the evening and on the morning before surgery General anaesthetic used: Induction: remifentanil infusion 0.4 µg/kg/minute, 5 minutes later propofol TCI, initially started at 3.5 µg/ml After intubation remifentanil reduced to constant rate of 0.2 µg/kg/minute Propofol TCI adjusted according to EEG target values or clinical variables 15 minutes before expected end of surgery propofol reduced in all groups to facilitate rapid emergence from anaesthesia; remifentanil infusion rate remained unchanged throughout end of surgery Regional anaesthesia used: NR Analgesia used: 100 ml infusion of 0.9% NaCl + metamizol 25 mg/kg for postoperative pain relief Muscle relaxants used: 0.1 mg/kg cisatracurium Antinausea drugs used: NR Other drugs used: hypotension treated with an i.v. vasopressor (Akrinor, 1 ml contains 100 mg of cafedrine and 5 mg of theodrenaline) given at dose chosen by investigator. Atropine 0.5 mg for bradycardia Type of surgery: minor orthopaedic surgery Duration of surgery: NR Duration of GA (minutes), mean (SD): group 1 = 121.2 (40.9); group 2 = 126.9 (67.7); group 3 = 108.2 (44.2) (reported in *table 1*, although text states this is duration of surgery) **Inclusion criteria:** ASA I, II, III adults 18–80 years scheduled to undergo minor orthopaedic surgery expected to last at least 1 hour **Exclusion criteria:** history of disabling central nervous or cerebrovascular disease, hypersensitivity to opioids or substance abuse, or a treatment with opioids or any psychoactive medication **Baseline measurements:** Sex (male), *n* (%): group 1 = 20/40 (50); group 2 = 20/40 (50); group 3 = 20/40 (50) Age (years), mean (SD): group 1 = 43.8 (4.2); group 2 = 44.8 (15.9); group 3 = 46.1 (14.5) Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 78.3 (13.8); group 2 = 76.6 (11.7); group 3 = 82.7 (17.8)	**Primary outcomes:** • Time taken to spontaneous opening of eyes **Secondary outcomes:** • Other outcomes reported – recovery times and consumption of remifentanil and propofol **Length of follow-up:** third day postoperative for recall **Methods of assessing outcomes:** End of surgery defined as final surgical suture when anaesthesia was stopped Emergence from anaesthesia defined as spontaneous opening of eyes, tracheal extubation and arrival at PACU Mean propofol infusion rate normalised to weight was calculated from induction and maintenance doses Intraoperative recall assessed by interview in PACU and on first and third postoperative day

Reviewer 1: JB Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		ASA grade, *n*, I/II/III: group 1 = 12/25/3; group 2 = 13/24/3; group 3 = 12/24/4 Risk factors for awareness: NR Comorbidities: NR **Losses to follow-up:** NR **Place of anaesthetic administration:** in the operating room	

NA, not reported; TCI, target-controlled infusion.

Outcome	Group 1 BIS	Group 2 Narcotrend	Group 3 Standard care	*p*-value
Intraoperative awareness/recall	0	0	0	
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR	
Time (minutes) to emergence from anaesthesia, mean (SD)	3.5 (2.9)*	3.4 (2.2)*	9.3 (5.2)	*$p<0.001$ Group1/2 vs group 3
Reduction compared with standard practice (%)	–63.4	–62.4	NA	
Time (minutes) to extubation, mean (SD)	4.1 (2.9)*	3.7 (2.2)*	9.7 (5.3)	*$p<0.001$ Group 1/2 vs group 3
Reduction compared with standard practice (%)	–57.7	–61.9	NA	
Time (minutes) to discharge to PACU, mean (SD)	7.0 (3.2)*	6.6 (2.8)*	12.4 (5.7)	*$p<0.001$ Group 1/2 vs group 3
Reduction compared with standard practice (%)	–43.5	–46.7	NA	
Anaesthetic consumption per patient				
Propofol (mg), mean (SD)	720.6 (245.3)*	721.3 (401.2)**	970.5 (384.4)	*$p<0.001$ **$p<0.05$
Reduction compared with standard practice (%)	–25.7	–25.7	NA	
Propofol (mg/kg/hour), mean (SD)	4.8 (1.0)*	4.5 (1.1)*	6.8 (1.2)	*$p<0.001$
Reduction compared with standard practice (%)	–29.4	–33.8	NA	
Normalised remifentanil infusion rates (µg/kg/minute), mean (SD)	0.22 (0.07)	0.21 (0.07)	0.20 (0.07)	ns
HRQoL	NR	NR	NR	
Nausea/vomiting/antisickness drugs	NR	NR	NR	
Pain/pain-relieving drugs	NR	NR	NR	
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR	
Mortality	NR	NR	NR	

NA, not applicable; NR, not reported.
The asterisk(s) refer to a statistical significance of 0.001 (*) or 0.05 (**).

Additional results/comments

Mean arterial blood pressure at various times points during anaesthesia similar between groups

Vasopressor was necessary in significantly more patients ($n = 27$) with standard practice than in Narcotrend ($n = 14$) or in the BIS group ($n = 17$) ($p < 0.05$). The mean drug amount was also significantly higher in the standard practice group

Five patients in each group needed 0.5 mg atropine for treatment of bradycardia

Recovery times were significantly shorter in women than men in the standard practice group with comparable amounts of propofol

Propofol consumption was significantly lower for men than women in the BIS group

BIS values comparable for patients in Narcotrend and BIS groups; significantly lower BIS values were observed in standard practice group vs BIS or Narcotrend group at various time points of anaesthesia

Methodological comments

Allocation to treatment groups: randomised by drawing lots from closed box

Allocation concealment: no details reported

Blinding: for standard practice group attending anaesthesiologist blinded to EEG readings; in EEG groups either only BIS or only Narcotrend monitor uncovered. Recovery times and propofol consumption recorded by a blinded investigator

Analysis by ITT: yes

Comparability of treatment groups at baseline: groups reported to be similar at baseline (no statistically significant differences reported)

Method of data analysis: for nominal data chi-squared test; for numerical data statistical analysis by *t*-test, Mann–Whitney *U*-test, or one-way analysis of variance with Student–Newman–Keuls test for multiple comparisons as appropriate; all tests two tailed with statistical significance defined as $p < 0.05$. Recovery time to opening of eyes also compared using Kaplan–Meier survival analysis

Sample size/power analysis: at least 26 patients had to be enrolled in each treatment group to provide 90% power to detect a difference of 3 minutes at $\alpha = 0.05$

Attrition/dropout: none reported

General comments

Generalisability: Sex differences observed within groups (see above). Results applicable to patients receiving i.v. GA with propofol–remifentanil for minor orthopaedic surgery

Intercentre variability: NA

Conflict of interests: NR

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Drawing lots
Allocation concealment	Unclear	Method not reported
Performance bias		
Blinding of participants and personnel	Unclear	Not all details reported; anaesthesiologist blinded
Detection bias		
Blinding of outcome assessment	Low	Blinded investigator for recovery times and propofol consumption
Attrition bias		
Incomplete outcome data	Low	ITT analysis
Reporting bias		
Selective reporting	Low	No evidence of selective reporting
Other bias		
Other sources of bias		

Reviewer 1: GF Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Lai *et al.*[59] **Year:** 2010 **Study design:** RCT **Number of centres:** one **Country:** China **Sponsor:** NR	**Group 1:** Narcotrend Narcotrend monitor (MonitorTechnik, Germany), with three-pole Blue sensor (Medicotest, Olstykke, Denmark) (skin impedance reported) Stated that vasoactive agents were used to target the appropriate NT range Target device/index value: Narcotrend (NT) index maintained between D_2 and E_0, then the fentanyl infusion rate was adjusted 10 minutes before end of surgery to target NT values between D_0 and D_1 Commencement of monitoring: not explicitly stated but appears to be the CT room (venue of the surgery) **Group 2:** standard clinical monitoring Monitoring of heart rate (normal = 50–100 b.p.m.), mean arterial pressure (normal = baseline value ± 20%) and body movement Length of experience/ training of anaesthetist: NR	**Total numbers involved:** 40; group 1, 20; group 2, 20 Premedication used: none reported General anaesthetic used (TIVA): Induction: Propofol 3 mg/kg/hour Maintenance: Propofol 4–8 mg/kg/hour Stated anaesthesia was lightened 10 minutes before the end of surgery (group 2; no further details provided) Regional anaesthesia used: none reported (local anaesthetic (lidocaine) used at the puncture site) Analgesia used: Induction: fentanyl 2 μg/kg Maintenance: fentanyl 1 μg/kg as necessary (see below); 10 minutes before end of surgery fentanyl was titrated to NT values between D0 and D1 (group 1) Muscle relaxants used: none (patients maintained spontaneous breathing) Antinausea drugs used: none reported Other drugs used: Tachycardia (> 100 b.p.m.): fentanyl 1 μg/kg, with metoprolol 1 mg added as necessary Hypertension (> 20% above baseline value): urapidil 10–15 mg Body movement: fentanyl 1 μg/kg Bradycardia (< 50 b.p.m.): atropine 0.2–0.5 mg Hypotension (> 20% below baseline value): ephedrine 5–10 mg Note: mentioned for group 1 only that if tachycardia, hypertension or body movement occurred, propofol infusion rate was increased as necessary Type of surgery: microwave coagulation for liver cancer Duration of surgery: NR Duration of GA (minutes) mean ± SD:[a] group 1, 91 ± 30; group 2, 88 ± 31; difference NS **Inclusion criteria:** patients with liver cancer scheduled to undergo microwave coagulation under the guidance of computed tomography (CT) **Exclusion criteria:** neurological or psychiatric problems; hearing defects; alcohol or drug dependence **Baseline measurements:** Sex (male), *n* (%): NR Age, years, mean (range): group 1, 44 (25–69); group 2, 41 (20–70); difference NS Ethnic groups, *n* (%): probably Chinese (NR)	**Outcomes (not stated whether primary or secondary):** • Changes in haemodynamic parameters • Arousal time • Recovery of orientation • Anaesthetic consumption • Postoperative nausea and vomiting • Intraoperative awareness • Postoperative (VASs) **Length of follow-up:** outcomes were assessed within 24 hours after surgery **Methods of assessing outcomes:** intraoperative awareness: stated that this was inquired within 24 hours after the operation, but no details of the method were provided Arousal time: defined as the time between cessation of drugs and the patient being able to open their eyes on command Time for recovery of orientation: defined as the time between a patient opening their eyes on command and the restoration of orientation Restoration of orientation: not defined VAS scores: no explanation of scale provided

Reviewer 1: GF Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Weight (kg) mean ± SD:[a] group 1, 60 ± 8; group 2, 60 ± 7; difference NS ASA grade: all patients were grade II to III Risk factors for awareness: none reported Comorbidities: Hypertension, *n* (%): group 1, 3 (15); group 2, 4 (20); difference NS **Losses to follow-up:** none reported; outcome data reported for all randomised patients (*n* = 20 per group) **Place of anaesthetic administration:** not explicitly stated but appears to be the CT room (venue of the surgery)	

b.p.m., beats per minute; CT, computed tomography; NR, not reported; NS, not statistically significant ($p > 0.05$); NT, Narcotrend index; SD, standard deviation.

Outcome[b]	Group 1 (*n* = 20)	Group 2 (*n* = 20)	*p*-value
Intraoperative awareness/recall			
Intraoperative awareness followed up 24 hours post surgery (no methodological details provided), *n* (%)	0 (0)	0 (0)	NA
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia, mean ± SD			
Arousal time	4.9 ± 2.2	9.5 ± 2.9	<0.01
Duration of orientation recovery	6.6 ± 3.2	12.2 ± 3.5	<0.01
Time to extubation	NA	NA	NA
Time to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption			
Propofol dose (mg), mean ± SD[c]	380 ± 35	460 ± 30	<0.01
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs			
Nausea or vomiting reported after surgery, *n* (%)	0 (0)	0 (0)	NA
Pain/pain relieving drugs			
Fentanyl dose, mg, mean ± SD[c]	0.15 ± 0.03	0.13 ± 0.03	0.68
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NA, not applicable; NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Stated there were no differences in heart rate or blood pressure between the two groups preoperation, at anaesthesia induction, at the beginning of surgery, at the end of surgery, or at anaesthesia emergence ($p > 0.05$) (data reported in charts, not extracted by reviewer)

Stated that the uses of vasoactive agents (ephedrine, atropine, metoprolol and urapidil) were not statistically different ($p > 0.05$) (no quantitative data reported)

Methodological comments

Allocation to treatment groups: stated random allocation but no details of sequence generation provided

Allocation concealment: NR

Blinding: NR

Analysis by ITT: not explicitly stated, but it appears that there were no withdrawals and that the outcomes data were reported for all randomised patients

Comparability of treatment groups at baseline: sex was not reported. Stated there was no significant difference between the two groups in terms of age, body weight, hypertension ($p > 0.05$)

Method of data analysis: stated that quantitative data were analysed with a chi-squared test and categorical data were analysed with independent *t*-tests or an analysis of variance. No other details of the analysis were reported

Sample size/power analysis: NR

Attrition/dropout: not explicitly reported but there do not appear to have been any dropouts

General comments

Generalisability: liver cancer patients eligible for microwave coagulation. Sex and ethnicity not reported, but appears to be a Chinese population. Early 40s in age, with ASA grade <III, most without concurrent hypertension, receiving TIVA with propofol and fentanyl. No specific risk factors for intraoperative awareness identified

Intercentre variability: NA (one centre)

Conflict of interests: NR

NA, not applicable; NR, not reported.

a Variance parameter not specified; assumed by reviewer to be SD.

b Postoperative VASs reported as an outcome: data not extracted by reviewer as no explanation or interpretation of the scores was provided.

c Not stated whether or not this was the total dose for all phases of anaesthesia.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Unclear	No information provided
Detection bias		
Blinding of outcome assessment	Unclear	No information provided
Attrition bias		
Incomplete outcome data	Low	Attrition not explicitly reported, but outcome data appear to have been reported for all randomised patients
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting
Other bias		
Other sources of bias	Unclear	The paper was translated from Chinese to English prior to publication. It is unclear whether or not any checks were made to ensure fidelity of the published version to the original work

Reviewer 1: GF Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Liao *et al.*[51] **Year:** 2011 **Study design:** RCT **Number of centres:** not reported but appears to be single centre **Country:** China **Sponsor:** supported in part by grants from Shin Kong Wu Ho-Su Memorial Hospital and Taipei Veterans General Hospital	**Group 1:** BIS, Philips BIS module (Aspect Medical Systems' XP platform technology) with Paediatric BIS Sensor Target device/index value: BIS 40–60 Commencement of monitoring: operating room Involved two anaesthesiologists, one of whom ensured proper functioning of the monitors during surgery **Group 2:** standard clinical practice Involved a single anaesthesiologist Goal: to maintain haemodynamic stability while avoiding patient movement and achieving a rapid recovery Group 3: auto-regressive index (AAI)-guided anaesthesia (data not extracted) Patients in all groups received both BIS and AAI sensors, and headphones, placed before induction in the operating room. In group 1, the AAI monitor was positioned out of the anaesthesiologist's line of sight. In group 2 the AAI and BIS monitors were positioned out of the anaesthesiologist's line of sight Length of experience/ training of anaesthetist: NR; all patients were induced by the same staff anaesthesiologist; patient behaviour during induction was assessed by a trained observer using the Induction Compliance Checklist (reference cited)	**Total numbers involved:** 160; group 1, 52. group 2, 54 (group 3, 54 – data not extracted) Premedication used: stated none GA used: inhaled: Induction: sevoflurane, initially 8 vol% fraction inspired with 50% N_2O in oxygen Maintenance: sevoflurane titrated by BIS values (group 1) or in 0.5% increments according to clinical signs (group 2), or in response to patient movement (either group) Recovery: sevoflurane was stopped at the time of the final surgical suture and fresh gas flow was increased Regional anaesthesia used: none reported Analgesia used: i.v. fentanyl 1 μg/kg 5 minutes before incision Muscle relaxants used: stated none (patients breathed spontaneously) Antinausea drugs used: none reported Other drugs used: in the PACU for patients who cried or suffered pain: meperidine 1.0 mg/kg; if agitation persisted, further meperidine 0.5 mg/kg and then midazolam 0.1 mg/kg (routes of administration not stated) Type of surgery: paediatric outpatient urologic surgery Duration of surgery, minutes, mean ± SD: group 1, 28.4 ± 11.2; group 2, 30.2 ± 14.0 (p = 0.70 for 3-group comparison) Duration of GA, minutes, mean ± SD: group 1, 39.5 ± 11.7; group 2, 41.8 ± 14.0 (p = 0.44 for three-group comparison) Duration of GA maintenance phase, minutes, mean ± SD: group 1, 36.8 ± 9.7; group 2, 38.7 ± 14.8 (p = 0.79 for three-group comparison) **Inclusion criteria:** pre-puberty children, aged 3–12 years, with ASA physical status I or II, scheduled for elective urologic outpatient surgery **Exclusion criteria:** history of premature delivery; reported developmental delay; deafness; significant cardiovascular, respiratory or neurological disease; receiving medication known to affect the central nervous system Baseline measurements (p-values refer to three-group comparisons; data for group 3 not extracted):	**Primary outcome:** • Recovery time (time to first spontaneous movement) **Secondary outcomes:** • Emergence delirium • Postoperative nausea and vomiting • Parental satisfaction • Anaesthetic consumption • Anaesthesia duration • Maintenance duration • Intraoperative recall • Device values • Haemodynamic parameters **Length of follow-up:** varied with outcome: up to 30 minutes after awakening for PACU; up to time of discharge for patient satisfaction; unclear for intraoperative recall (nurses appear to have assessed this at a separate follow-up interview, the date of which was not reported) **Methods of assessing outcomes:** Anaesthesia time: defined as the time from induction to discontinuation Sevoflurane maintenance time: defined as the time from insertion of laryngeal mask airway to discontinuation of sevoflurane Surgery time: defined as the time from incision to the final surgical suture End of surgery: defined as the time of the final surgical suture Responses: times of first movement response, phonation or eye-opening were assessed after discontinuation of sevoflurane (i.e. after the final surgical suture)

Reviewer 1: GF Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Sex (male), *n* (%): group 1, 41 (79); group 2, 45 (83); $p = 0.15$ Age, years, mean ± SD: group 1, 6.0 ± 2.8; group 2, 6.1 ± 2.8; $p = 0.39$ Ethnic groups: probably Chinese (NR) Weight (kg) mean ± SD: group 1, 24.7 ± 11.1; group 2, 23.5 ± 9.3; $p = 0.54$ Height, cm, mean ± SD: group 1, 116.7 ± 17.5; group 2, 115.8 ± 15.4; $p = 0.52$ BMI, kg/m^2, mean ± SD: group 1, 16.4 ± 3.2; group 2, 16.3 ± 2.5; $p = 0.88$ ASA grade I/II, *n*: group 1, 46/6; group 2, 50/4; $p = 0.74$ Risk factors for awareness: none specifically reported Comorbidities: none reported **Losses to follow-up:** none reported **Place of anaesthetic administration:** induction commenced in a pre-anaesthetic clinic; full anaesthetic given in the operating room	PAED score (reference cited): assessed by a trained observer in the PACU every 5 minutes after awakening for 30 minutes. The highest score during this period was used in the final PAED score Readiness for PACU discharge (= full hospital discharge): defined as a score of 9 or more, with no zeros in any domains, on the Aldrete score, and a room air O_2 saturation of ≥96% Intraoperative recall: patients were asked at a follow-up interview (timing not specified) by a nurse of the Anaesthesia Department of the hospital whether they could recall any event or dreaming during the intraoperative period Parent satisfaction with child's treatment: assessed at PACU discharge and rated on a scale from very good, good, acceptable to a bad experience

NR, not reported.

Outcome	Group 1 ($n = 52$)	Group 2 ($n = 54$)	*p*-value (a) for three-group comparison; (b) post hoc comparison group 1 v group 2
Intraoperative awareness with explicit recall, *n* (%)	0 (0)	0 (0)	NA
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia, mean ± SD:			
Spontaneous movement	3.6 ± 2.7	6.1 ± 5.7	(a) 0.02; (b) <0.05
Phonation	8.4 ± 5.2	12.9 ± 9.0	(a) 0.11
Eyes opening	15.0 ± 16.4	16.1 ± 11.3	(a) 0.17
Time to extubation: NA			
Time (minutes) to laryngeal mask airway removal, mean ± SD	1.8 ± 1.6	2.1 ± 2.4	(a) 0.93
Time (minutes) to discharge from the recovery room, mean ± SD	64.5 ± 10.1	66.8 ± 9.0	(a) 0.03; (b) <0.05
Anaesthetic consumption			
Sevoflurane, (g/minute), mean ± SD	0.6 ± 0.2	0.9 ± 0.3	(a) <0.001; (b) <0.01
Mean end-tidal sevoflurane concentration,%, during maintenance	2.5 ± 0.4	2.9 ± 0.5	(a) 0.001 (b) <0.01
(See also additional comments below concerning anaesthetic consumption at different time points)			
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs			
Postoperative nausea, *n* (%)	5 (10)	6 (11)[a]	(a) 0.95
Postoperative vomiting, *n* (%)	2 (4)	3 (6)[a]	(a) 0.88
Pain/pain relieving drugs, *n* (%)			
Did not receive analgesic or sedative agents	4 (8)[a]	5 (9)	(a) 0.83
Rescue requiring more analgesic or sedative agents	9 (17)	6 (11)[a]	(b) 0.6
Fentanyl use (μg) mean ± SD	24.8 ± 11.1	23.4 ± 9.1	(a) 0.54
Other morbidity			
PAED score, median (interquartile range)	18 (14–16)	15 (13–15)	(a) 0.94
Mortality, *n* (%)	0 (0)	0 (0)	NA

NA, not applicable; NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Baseline data were reported for the number (%) of patients in each group who underwent the following types of surgery: herniorrhaphy; circumcision; herniorrhaphy and circumcision; orchiopexy; hydrocelectomy; varicocele ligation (p-values for three-group comparisons of these variables all >0.7; data not extracted). Baseline data were also reported for the BMI-for-age percentile (three-group comparison, $p = 0.52$) and Induction Compliance Checklist score (three-group comparison, $p = 0.96$) (data not extracted)

Mean arterial pressure did not differ significantly between the groups at baseline ($p \geq 0.05$), but was significantly higher in group 1 than group 2 during and at the end of surgery ($p < 0.01$) (reported in a graph; data not extracted)

Mean heart rate and mean respiratory rate did not differ significantly between the groups at any time point ($p \geq 0.05$) (data not reported)

Mean end-tidal sevoflurane concentration (%) was reported in a graph for six time points from start of induction to end of surgery and was significantly higher ($p < 0.01$) in group 1 than group 2 at four times: at the start of surgery; 5 minutes after incision; 10 minutes after incision; and at the end of surgery (data not extracted)

The number (%) of patients who moved during surgery was 11 (21) in group 1 and 10 (19) in group 2 ($p = 0.94$ for three-group comparison)

The number (%) of patients whose parents gave a satisfaction score of very good, good, acceptable or bad was reported and did not differ significantly between the groups ($p = 1.00$ for each rating class; there were no bad experiences reported) (data not extracted)

Stated there were no adverse respiratory events in any of the groups

Methodological comments

Allocation to treatment groups: patients were allocated randomly to three groups after induction of anaesthesia, using a computer-generated randomisation table

Allocation concealment: NR

Blinding: two anaesthesiologists were involved in the study, a third investigator assessed the patient during the emergence and recovery period, and a nurse of the Anaesthesia Department assessed intraoperative recall at a follow-up interview. Stated that both anaesthesiologists were blinded to the anaesthetic technique and all three investigators were blinded to the grouping of the patient. However, the methods used to achieve blinding were not reported, and it was not stated whether or not the nurse who assessed intraoperative recall was blinded to the patient group

Analysis by ITT: not reported, but there appears to have been no attrition; all randomised patients would appear to have been analysed

Comparability of treatment groups at baseline: groups appear comparable for age, weight, ASA health status, types of surgery being undertaken and haemodynamic parameters; no statistically significant differences were reported at baseline

Method of data analysis: group comparisons of continuous variables were made by one-way analysis of variance for normally distributed variables or by Kruskal–Wallis rank-sum test for non-normally distributed variables. Where differences were significant, post hoc comparisons between groups were by Bonferroni correction (normally distributed variables) or by Mann–Whitney U-test (non-normally distributed variables). Categorical data were analysed by chi-squared or Fisher's exact test as appropriate

Sample size/power analysis: stated that an a priori power analysis was based on a previous study (Bannister *et al.*[45]) which suggested that a sample size of 44 patients for each group should be adequate to achieve a 30% or greater reduction in the time to first movement response with a power of 0.9 ($\alpha = 0.05$)

Attrition/dropout: none reported, but sample sizes for postoperative outcomes suggest there were no dropouts

General comments

Generalisability: pre-pubertal predominantly male, probably Chinese, paediatric outpatient population with ASA health status <3, who received GA with sevoflurane. Not identified as being at high risk of intraoperative awareness

Intercentre variability: NA (appears to be one centre)

Conflict of interests: NR

NA, not applicable; NR, not reported.

a Rounded percentage as calculated by reviewer (difference of 1% from that reported by the authors).

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Randomisation sequence generated by computer
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Unclear	Stated that both anaesthesiologists were blinded to the anaesthetic technique and all three investigators were blinded to the grouping of the patient. However, the methods used to achieve blinding were not reported so it is unclear how easily blinding could be broken
Detection bias		
Blinding of outcome assessment	Low	Not reported whether or not the nurse who assessed intraoperative recall was blinded. The investigator who assessed other outcomes was blinded (method of blinding not reported)
Attrition bias		
Incomplete outcome data	Low	None reported, but sample sizes for postoperative outcomes suggest there were no dropouts
Reporting bias		
Selective reporting	Low	No evidence to suggest reporting bias

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Reviewer 1: JS Reviewer 2: GF			
Reference and design	**Technology**	**Participants**	**Outcome measures**
Author: Messieha *et al*.[52] **Year:** 2004 **Study design:** RCT **Number of centres:** one (presumed) **Country:** USA **Sponsor:** not stated	**Group 1:** 'BIS known' – BIS (Aspect Medical Systems), no further detail given Target device/index value: 60-70 Adjustment of inhalation anaesthetic also based on patient vital signs (heart rate, blood pressure, surgical stimulation) **Group 2:** 'BIS unknown' Adjustment of inhalation anaesthetic based on patient vital signs (heart rate, blood pressure, surgical stimulation) BIS was recorded but anaesthesiologist was not aware of the BIS number Commencement of monitoring: not stated when monitoring started, but BIS was continued until PACU discharge Length of experience/ training of anaesthetist: not stated	**Total numbers involved:** 20 children recruited, 10 in each study arm Premedication used: ketamine 3 mg/kg; midazolam 0.05 mg/kg; glycopyrrolate 0.2 mg, intramuscular injection General anaesthetic used: sevoflurane, dose not stated Regional anaesthesia used: none stated Analgesia used: fentanyl, 1 µg/kg (maintenance) Muscle relaxants used: rocuronium bromide 1 mg/kg Antinausea drugs used: ondansetron 0.15 mg/kg, given near the end of the procedure Other drugs used: none stated Type of surgery: complete dental rehabilitation Duration of surgery (minutes), mean (SD): group 1 = 139 (± 43); group 2 = 162 (± 35); $p = 0.2$ Duration of GA: not stated **Inclusion criteria:** scheduled to undergo complete dental rehabilitation under general anaesthetic. Patients with mild cerebral palsy without significant neurological deficit also enrolled **Exclusion criteria:** none stated **Baseline measurements:** Sex (male), *n* (%): group 1 = 4 (40); group 2 = 7 (70) ($p = 0.3$) Age (years), mean (SD): group 1 = 7.4 (± 3), range 3–13 years; group 2 = 5.5 (± 3), range 2-12 years ($p = 0.2$) Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 28 (± 15); group 2 = 21 (± 9); $p = 0.2$ ASA physical status grade, mean (range): group 1 = II (I–III); group 2 = II (I–III); $p = 1.0$ Risk factors for awareness: none reported Comorbidities – cerebral palsy, *n* (%): group 1 = 2 (20%); group 2 = 2 (20%); $p = 1.0$ **Losses to follow-up:** NR **Place of anaesthetic administration:** presedation was given prior to transfer to the operating room. Upon transfer GA was started	**Primary outcome:** • Study focused on the reduction in time from end of general anaesthesia to extubation and to PACU discharge **Secondary outcomes:** • Length of PACU stay • Duration of surgery • BIS values **Length of follow-up:** not stated **Methods of assessing outcomes:** not stated other than BIS values were recorded by an independent observer. Not clear whether or not assessment of other outcomes was blinded

NR, not reported.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia	NR	NR	NR
Time (minutes) to extubation, mean (SD)	9 (± 5)	13 (± 5)	0.07
Time (minutes) to PACU discharge, mean (SD)	60 (± 13)	90 (± 11)	<0.001
Duration (minutes) of PACU stay, mean (SD)	45 (± 8)	71 (± 9)	<0.001
Anaesthetic consumption	NR	NR	NR
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; SD, standard deviation.

Additional results/comments

BIS values recorded at key points before, during and after the surgical and anaesthetic procedure showed no statistically significant differences between groups

Duration of surgery did not differ statistically significantly between the two study arms

The level of the surgical care and the procedure were similar in all patients

Methodological comments

Allocation to treatment groups: random, no further information given

Allocation concealment: NR

Blinding: describes the study as observer blind, but no other information provided. Presume that the observer recording BIS values was not aware of allocation to study arm

Analysis by ITT: NR

Comparability of treatment groups at baseline: described as comparable. No statistically significant differences reported between groups at baseline

Method of data analysis: student's *t*-test and Mann–Whitney rank-sum test

Sample size/power analysis: NR

Attrition/dropout: NR

General comments

Generalisability: relevant to US paediatric patients undergoing dental procedures under general anaesthetic with use of premedication and muscle relaxant. Not clear which version of the BIS module was used, so results may not necessarily be comparable to studies using later or earlier versions

Intercentre variability: NA (presumed to be one centre)

Conflict of interests: NR

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given on the randomisation method used
Allocation concealment	Unclear	NR
Performance bias		
Blinding of participants and personnel	Unclear	NR
Detection bias		
Blinding of outcome assessment	Unclear	BIS values recorded by blinded observer. Not clear whether or not assessment of other outcomes was blinded
Attrition bias		
Incomplete outcome data	Unclear	NR
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

NR, not reported.

Reviewer 1: JS Reviewer 2: GF

Reference and design	Technology	Participants	Outcome measures
Author: Messieha *et al.*[53] **Year:** 2005 **Study design:** RCT **Number of centres:** one (presumed) **Country:** USA **Sponsor:** not stated	**Group 1:** 'BIS known' – BIS (Aspect Medical Systems), no further detail given Target device/index value: 55-65 Adjustment of inhalation anaesthetic also based on patient vital signs (heart rate, blood pressure, surgical stimulation) **Group 2:** 'BIS unknown' Adjustment of inhalation anaesthetic based on patient vital signs (heart rate, blood pressure, surgical stimulation) BIS was recorded but anaesthesiologist was not aware of the BIS number End-tidal carbon dioxide maintained at the standard operation room level of 30–35 in all patients (both groups) Commencement of monitoring: not stated when monitoring started, but BIS was continued until PACU discharge Length of experience/ training of anaesthetist: not stated	**Total numbers involved:** 29 children recruited; group 1 = 15; group 2 = 14 Premedication used: Versed (midazolam) 0.7 mg/kg orally General anaesthetic used: titrated sevoflurane, dose not stated Regional anaesthesia used: none stated Analgesia used: fentanyl, 1 μg/kg, i.v. administered at the start of the case Muscle relaxants used: rocuronium bromide 1 mg/kg, single dose administered at the beginning of the case. Reversal was administered at the end of the case (drug not stated) Antinausea drugs used: ondansetron 0.15 mg/kg, i.v. Other drugs used: none stated Type of surgery: complete dental rehabilitation Duration of surgery (minutes), mean (SD): group 1 = 133 (± 31); group 2 = 143 (± 33) Duration of GA: not stated **Inclusion criteria:** aged 2–18 years, scheduled to undergo complete dental rehabilitation under general anaesthetic. Patients with mild cerebral palsy without significant neurological deficit also enrolled **Exclusion criteria:** none stated **Baseline measurements:** Sex male–female ratio: group 1 = 4 : 10; group 2 = 2 : 3 (numbers not reported) Age (years), mean (SD): group 1 = 4 (± 2); group 2 = 4 (± 2) Ethnic groups, *n* (%): NR Weight (kg), mean (SD): group 1 = 17 (± 5); group 2 = 18 (± 5) ASA physical status grade: group 1 = I–II; group 2 = I–II Risk factors for awareness: none reported Comorbidities – Children with mild cerebral palsy were eligible, but it is not stated how many were included **Losses to follow-up:** NR **Place of anaesthetic administration:** presedation was given 15–20 minutes prior to transfer to the operating room. Upon transfer GA was started	**Primary outcome:** • Purpose of the study to evaluate time to extubation (from the end of general anaesthetic or turning off the sevoflurane) and time between anaesthesia termination and discharge from PACU **Secondary outcomes:** • Length of PACU stay • Duration of surgery • BIS values **Length of follow-up:** not stated **Methods of assessing outcomes:** criteria for discharge from PACU included consciousness, normal vital signs, no pain, no nausea or vomiting, ability to pass urine BIS values were recorded by an independent observer. Not clear whether or not assessment of other outcomes was blinded

NR, not reported.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	NR	NR	NR
Time (minutes) to extubation, mean (SD)	5 (± 2)	10 (± 7)	0.04
Duration (minutes) of PACU stay, mean (SD)	47 (± 17)	63 (± 17)	0.02
Anaesthetic consumption	NR	NR	NR
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported; SD, standard deviation.

Additional results/comments

States that none of the patients experienced postoperative pain or postoperative nausea and vomiting

BIS values recorded at key points before, during and after the surgical and anaesthetic procedure in both arms showed no statistical significance

Duration of surgery did not differ statistically significantly between the two study arms

Stated that the level of the surgical care and the procedure were similar in all patients

Methodological comments

Allocation to treatment groups: random, no further information given

Allocation concealment: NR

Blinding: describes the study as observer blind, but no other information provided. The observer recorded BIS values. Unclear whether or not the measurement of other outcomes was blinded

Analysis by ITT: not reported and not discernible (attrition not reported)

Comparability of treatment groups at baseline: described by authors as comparable in terms of ASA physical status, weight and sex

Method of data analysis: *t*-test and Mann–Whitney rank-sum test

Sample size/power analysis: NR

Attrition/dropout: NR

General comments

Generalisability: relevant to US paediatric patients undergoing dental procedures under general anaesthetic with sevoflurane with use of oral premedication. Ethnicity not stated; no specific risk factors for intraoperative awareness

Intercentre variability: NA (presumed to be one centre)

Conflict of interests: NR

NA, not applicable; NR, not reported.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information given on the randomisation method used
Allocation concealment	Unclear	NR
Performance bias		
Blinding of participants and personnel	Unclear	NR
Detection bias		
Blinding of outcome assessment	Unclear	BIS values recorded by blinded observer. Not clear whether or not assessment of other outcomes was blinded
Attrition bias		
Incomplete outcome data	Unclear	NR
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

NR, not reported.

Reviewer 1: GF Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Rundshagen *et al.*[60] **Year:** 2007 **Study design:** RCT **Number of centres:** not stated (appears to be single) **Country:** not stated, appears to be Germany (multinational authors) **Sponsor:** study supported by Astra Zeneca and a university institutional research grant	**Group 1:** Narcotrend (NCT) (Narcotrend Monitor version 2.0 AF; MonitorTechnik, Bad Bramstedt, Germany; with Blue Sensor; Medicotest S/A, Istykke, Denmark) Target device/index value: NCT D2 – E0 If outside target NCT level, protocol was to first adapt the stepwise target-controlled propofol infusion ± 0.5 µg/kg/minute then the remifentanil infusion ± 0.1 µg/kg/minute Commencement of monitoring: 5–10 minutes before induction of anaesthesia **Group 2:** standard clinical practice (anaesthesia guided by clinical parameters according to the individual decision of the anaesthetist) Both groups: implied (not stated explicitly) that BIS (A-2000TM, version 2.21; Aspect Medical Systems) and NCT were both monitored, with the anaesthesiologist being blinded to BIS values in group 1 and blinded to both BIS and NCT values in group 2 Length of experience/ training of anaesthetist: stated that all patients were treated by one experienced consultant anaesthetist; no details provided	**Total numbers involved:** 48; group 1, 24; group 2, 20 (after attrition) Premedication used: midazolam 0.1 mg/kg orally, 45 minutes pre surgery General anaesthetic used (i.v.): Induction: remifentanil 0.5 µg/kg/minute continuous infusion followed 1 minute later by target-controlled infusion of propofol, with an estimated plasma concentration 3 µg/ml Maintenance: remifentanil and propofol (doses not stated). FIO_2 was kept at 0.3 (except for one-lung ventilation: 1.0 then 0.5 if blood gas analysis acceptable) Regional anaesthesia used: none reported Analgesia used: novaminsulfone 2 g for 20 minutes before and piritramide 7.5 mg for 5 minutes before the suggested end of surgery. Piritramide or morphine (doses not stated) as needed for early postoperative pain in PACU Muscle relaxants used: rocuronium 0.6 mg/kg, before intubation Antinausea drugs used: metoclompramid (dose not stated) used as rescue medication for nausea Other drugs used: see additional comments for full list Type of surgery: stated only that patients were undergoing all kinds of elective surgery, which included surgery for 'malignoma' and peripheral vascular surgery Duration of surgery: NR Duration of GA (minutes) mean ± SD: group 1, 111.1 ± 59.36; group 2, 104.75 ± 54.01; $p = 0.712$ **Inclusion criteria:** none reported **Exclusion criteria:** neurological diseases; consumption of medication affecting the central nervous system; cardiac surgery; neurosurgery; history of drug dependence; alcoholism; pregnancy; or a known intolerance of the used drugs **Baseline measurements:** Sex, male, *n* (%): group 1, 8 (33); group 2, 8 (40); $p = 0.651$ Age, years, mean: group 1, 48.8 (maximum 70); group 2, 58 (maximum 78); $p = 0.041$ Ethnic groups, *n* (%): NR Weight (kg) mean ± SD: group 1, 80.2 ± 17.19; group 2, 77.7 ± 23.03; $p = 0.680$ ASA grade I/II/III (*n*): group 1, 6/12/4; group 2, 4/13/3; $p = 0.836$	**Primary (powered) outcome:** • Time to extubation **Secondary outcomes:** • Postoperative nausea and fatigue • Total anaesthetic doses • Duration of anaesthesia • Memory during anaesthesia • Clinical parameters (heart rate, pulse oximetry, rectal temperature, end-expiratory CO_2, systolic and diastolic arterial pressure) • NCT and BIS values **Length of follow-up:** longest follow-up appears to be on the first postoperative day (for memory questioning) **Methods of assessing outcomes:** plasma propofol concentration was analysed by high-performance liquid chromatography (details of method, calibration and validation reported) Postoperative nausea and fatigue was assessed after 10, 30 and 90 minutes in the PACU using a 100-mm VAS (no details of scaling given) Memory during anaesthesia was assessed by questioning the patient on the first postoperative day (no details of method given) Heart rate, pulse oximetry, rectal temperature, and end-expiratory CO_2 were measured continuously (Ohmeda Modulus CD; Madison, WI, USA) NCT and BIS values were recorded continuously and stored for off-line analyses

Reviewer 1: GF Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Risk factors for awareness: none reported Comorbidities: none reported that would be likely to affect EEG (for other comorbidities see additional comments) Losses to follow up: NR. Attrition reported but unclear whether pre or post randomisation **Place of anaesthetic administration:** GA was induced upon arrival in the operating room	

NR, not reported.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall			
Explicit memory during anaesthesia, *n* (%)	0 (0)	0 (0)	NR
Recalled dreaming during anaesthesia, *n* (%)	2 (8)	0 (0)	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	NR	NR	NR
Time (minutes) to extubation, mean ± SD	10.6 ± 7.19	9.29 ± 6.23	0.525
Time to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption			
Propofol dose (μg/kg/minute), mean ± SD	0.093 ± 0.042	0.114 ± 0.035	0.089
Remifentanil dose (μg/kg/minute), mean ± SD	0.31 ± 0.10	0.34 ± 0.11	0.449
Propofol plasma concentration, μg/ml, mean ± SD[a]			
Intubation	3.7 ± 1.6	2.9 ± 1.4	>0.05
Skin incision	3.4 ± 1.5	3.1 ± 1.2	>0.05
Extubation	1.5 ± 1.3	1.5 ± 1.4	>0.05
10 minutes after extubation	1.5 ± 1.6	1.0 ± 0.9	>0.05
90 minutes after extubation	0.9 ± 1.3	0.7 ± 1.0	>0.05
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs			
Nausea and fatigue VAS scores, mean ± SD[b]			
Nausea, 10 minutes post surgery	6.88 ± 15.2	24.06 ± 34.04	0.005
Nausea, 30 minutes post surgery	15.44 ± 23.8	18.58 ± 24.9	0.146
Nausea, 90 minutes post surgery	9.18 ± 19.0	12.00 ± 27.4	0.095
Fatigue, 10 minutes post surgery	47.74 ± 20.7	45.31 ± 18.9	0.740
Fatigue, 30 minutes post surgery	57.30 ± 22.4	46.32 ± 23.3	0.088
Fatigue, 90 minutes post surgery	74.73 ± 22.5	63.00 ± 30.2	0.164
Metoclopramid for nausea, *n* (%)	1 (4)	3 (15)	NR
Pain/pain-relieving drugs			
Morphine in PACU, *n* (%)	3 (13)	3 (15)	NR
Piritramide in PACU, *n* (%)	10 (42)	8 (40)	NR
Morphine dose in PACU (mg), mean ± SD[a]	5 ± 0	8 ± 3	NR
Piritramide dose in PACU (mg), mean ± SD[a]	6 ± 2	7 ± 3	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Baseline data for patients' height, type of operation (peripheral/abdominal/thorax), and Apfel score (risk of postoperative nausea and vomiting) were reported; *p*-values for inter-group differences were all >0.05

Four patients in group 1 (17%) and five patients in group 2 (25%) required surgery because of 'malignoma', but none received preoperative radiation or chemotherapy

Changes in the anaesthetic regimen (titration of dose up or down) were reported for propofol and remifentanil (data not extracted); differences between the study groups were not statistically significant ($p > 0.05$)

Average temperature during anaesthesia was reported and was identical in both study groups

Stated that all patients except one were extubated earlier in group 1

Other drugs used during anaesthesia:

Theoadrenaline plus cafedrine (Akrinor) (doses reported), *n* (%): group 1, 14 (58%); group 2, 12 (60%)

Atropine 0.5 mg during induction, *n* (%): group 1, 2 (8); group 2, 0 (0)

Dopamine 1–5 mg/kg/minute to maintain mean arterial pressure >80 mmHg (peripheral vascular surgery patients only), *n* (%): group 1, 4 (17); group 2, 2 (10)

Nitroglycerin spray (antihypertensive), *n* (%): group 1, 1 (4); group 2, 0 (0)

Urapidil 20 mg (antihypertensive), *n* (%): group 1, 1 (4); group 2, 0 (0)

Clonidine 75–150 µg during extubation, *n* (%): group 1, 2 (8); group 2, 2 (10)

Variances of diastolic blood pressure and mean arterial pressure were significantly larger in group 2 ($p \leq 0.034$ for both parameters combined), but the combined difference was not significant when age-corrected data were analysed

Comorbidities requiring perioperative medication:

Arterial hypertension, *n* (%): group 1, 6 (25); group 2, 4 (20)

Cardiac arrhythmia, *n* (%): group 1, 3 (13); group 2, 2 (10)

Diabetes type II, *n* (%): group 1, 1 (4); group 2, 2 (10)

Asthma, *n* (%): group 1, 3 (13); group 2, 0 (0)

Miscellaneous, *n* (%): group 1, 7 (29); group 2, 3 (15)

None, *n* (%): group 1, 5 (21); group 2, 8 (40)

Methodological comments

Allocation to treatment groups: stated random allocation but no details provided

Allocation concealment: NR

Blinding: NR

Analysis by ITT: unclear. Analysis does not include all the patients who started but it is unclear whether or not attrition happened pre or post randomisation

Comparability of treatment groups at baseline: groups were similar for the reported variables of sex, height, weight, ASA physical status, type of operation and risk of postoperative nausea and vomiting (Apfel score). However, patients were slightly younger in group 1 ($p = 0.041$) (data given above) and no information on ethnicity was provided

Method of data analysis: normality of distribution was tested for all variables using a Kolmogorov–Smirnov test. Intergroup comparisons for propofol concentrations and visual analogue scores were tested by repeated-measures analysis of variance or non-parametric statistics. Intergroup comparisons for time of anaesthesia, doses of anaesthetics and times to extubation were tested by Mann–Whitney *U*-test. Effects of patients' characteristics were tested by analysis of variance and a posteriori Scheffé test. EEG parameters were adjusted for patient characteristics

Sample size/power analysis: To achieve a power of at least 80%, standard deviations of the mean difference in time to extubation reported by Kreuer *et al.*[63] were utilised for comparisons between BIS, NCT and standard clinical practice. Given $\alpha = 5\%$, and $d = 1.0$, the required sample size was estimated using a power table to be 13 subjects per group

Attrition/dropout: stated that out of 48 patients, the data for 44 patients were included in the final analyses. Reasons for four withdrawals were reported, but it was not stated the withdrawals occurred pre or post randomisation nor how they were distributed among the two study groups

Generalisability: appears to be a German adult population, predominantly of ASA grade II, but some grade I and III, with cardiovascular comorbidities, undergoing various elective surgical procedures, and receiving propofol and remifentanil GA. Ethnicity not reported. No explicit risk factors for intraoperative awareness identifiable

Intercentre variability: NA (appears to be a single-centre study)

Conflict of interests: none reported

NA, not applicable; NR, not reported.

a Assumed by reviewers to be mean and SD values (not explicitly stated).

b Direction of scale not reported: assumed higher values indicate worse nausea and fatigue.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Unclear	No information provided
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Unclear	No information provided
Detection bias		
Blinding of outcome assessment	Unclear	No information provided
Attrition bias		
Incomplete outcome data	Unclear	Attrition reasons reported but distribution of attrition across study groups not reported. Unclear whether attrition was pre or post randomisation
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

Reviewer 1: GF Reviewer 2: JB

Reference and design	Technology	Participants	Outcome measures
Author: Talawar *et al.*[56] **Year:** 2010 **Study design:** RCT **Number of centres:** one **Country:** India **Sponsor:** stated no external funding used	**Group 1:** E-Entropy (S/5 Avance; GE Healthcare, Datex-Ohmeda Division, Helsinki, Finland) Target device/ index value: state entropy between 45 and 65 during the procedure and between 65 and 70 during the last 15 minutes of surgery Commencement of monitoring: In operating room after anaesthesia induction **Group 2:** 'Control' Anaesthesia was titrated to maintain heart rate and mean arterial pressure within 20% of baseline. Simultaneously monitored entropy values were obscured from the anaesthesiologist Length of experience/training of anaesthetist: NR	**Total numbers involved:** 50; group 1, 25; group 2, 25 Premedication used: none reported General anaesthetic used: Induction: i.v. propofol 3–5 mg/kg for patients with an i.v. line in situ; otherwise inhaled sevoflurane in N_2O and O_2 (50 : 50). Patients receiving propofol/ sevoflurane (*n*/*n*) for induction were: group 1, 14/11; group 2, 17/8 (difference: $p = 0.38$) Maintenance: N_2O, O_2 (50 : 50) and isoflurane at inspired concentration 1% (0.8– 0.9 MAC) with 1 l-flow once steady state achieved. Group 2 only: anaesthetic concentration was increased to 1.3 MAC if movement in response to surgical stimulation, lacrimation, or an increase in heart rate or mean arterial pressure by 20% occurred Recovery: inhalational agent was discontinued after skin closure Regional anaesthesia used: caudal block using 0.25% bupivacaine 0.75–1 ml/kg Analgesia used: i.v. fentanyl 1 µg/kg (appears to be after insertion of the laryngeal mask airway) Maintenance: i.v. fentanyl 0.5 µg/kg was administered if the state entropy–response entropy difference increased by more than 10 (group 1), or if signs did not subside or haemodynamic parameters did not settle after increasing the inhaled anaesthesia to 1.3 MAC (group 2) Post surgery: children with a pain score of ≥6 were administered i.v. boluses of fentanyl 0.5 µg/kg every 10 minutes until pain subsided Muscle relaxants used: none used Antinausea drugs used: none reported Other drugs used: none reported Type of surgery: lower abdominal or urological day care surgery Duration of surgery, minutes, median (range): group 1, 29 (16–95); group 2, 30 (15–94); difference $p = 0.47$ Duration of GA, minutes, median (range): group 1, 68 (32–125); group 2, 72 (47–180); difference $p = 0.23$ **Inclusion criteria:** patients undergoing lower abdominal or urological day care surgery between March 2006 and March 2008. No other criteria reported **Exclusion criteria:** parents refused consent; known neurological disorder; history of major head injury; on antiepileptic drugs; any contraindications to laryngeal mask airway insertion	**Primary (powered) outcome:** • Time to awakening **Secondary outcomes:** • Device values • Haemodynamic parameters (ECG, blood pressure, O_2 saturation, end-tidal CO_2 concentration) • End tidal anaesthesia concentration • Recovery score • Time to discharge for PACU • Postoperative pain score **Length of follow-up:** longest duration of follow-up appears to be up to 2 hours in the recovery area for pain assessment **Methods of assessing outcomes:** Blood pressure was assessed non-invasively Time to awakening was the period from discontinuation of anaesthesia Awakening was defined as spontaneous eye-opening, the onset of purposeful limb movements or phonation Recovery was assessed according to modified Steward Recovery score (reference cited); the time to achieve a maximal Steward score was recorded Time to discharge for PACU was the time to transfer from the operating theatre after switching off inhalational anaesthetic agents Pain was assessed in the recovery area by CHEOPS (reference cited) every 30 minutes for the first 2 hours. Note non-independence of postoperative analgesia and postoperative pain scores (see left)

Reviewer 1: GF Reviewer 2: JB			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Baseline measurements: Sex (male), *n* (%): group 1, 25 (100); group 2, 22 (88); difference $p = 0.52$ Age, years, median (range): group 1, 4 (2–12); group 2, 5 (2–11); difference $p = 0.73$ Ethnic groups, *n* (%): NR Weight, kg, median (range): group 1, 16 (8–28); group 2, 16 (9–40); difference $p = 0.07$ ASA grade: I and II (not reported separately by group) Risk factors for awareness: none reported Comorbidities: none reported **Losses to follow-up:** none reported (all patients included in analysis) **Place of anaesthetic administration:** operating room	

NR, not reported.

Outcome	Group 1	Group 2	*p*-value (mean difference for parameter; 95% CI)
Intraoperative awareness/recall	NR	NR	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia			
Recovery time (time to awakening), median (range)	7 (3–18)	10 (5–21)	0.017
Recovery time (time to awakening), mean ± SD	8.2 ± 4.49	10.96 ± 3.86	(2.72; 0.34 to 5.1)
Time to reach Steward score of 6, median (range)	6 (1–15)	8 (2–24)	0.464
Time to reach Steward score of 6, mean ± SD	7.08 ± 3.78	8.36 ± 4.8	(1.3; –1.2 to 3.7)
Time to extubation	Not applicable	Not applicable	Not applicable
Time (minutes) to discharge to/from the recovery room			
Time to discharge for PACU, median (range)	15 (5–31)	19 (10–40)	0.045
Time to discharge for PACU, mean ± SD	15.32 ± 6.6	19.32 ± 7.12	(4.0; 0.07 to 7.9)
Anaesthetic (isoflurane) consumption (%) mean[a]			
Immediately before laryngeal mask airway Laryngeal mask airway insertion	0.81	1.24	<0.05
15 seconds after LMA insertion	0.78	1.24	<0.05
15 seconds after caudal analgesia	0.69	0.84	<0.05
15 seconds after skin incision	0.68	0.78	<0.05
5 minutes after skin incision	0.68	0.79	<0.05
Immediately before removal	0.35	0.38	≥0.05
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain relieving drugs			
Postoperative pain scores, mean (standard error)			
30 minutes after admission to PACU	4.88 (0.319)	4.76 (0.09)	0.71 (0.12; –0.53 to 0.77)
60 minutes	4.48 (0.10)	4.76 (0.08)	0.01 (–0.28; 4.59 to 4.92)[b]
90 minutes	4.56 (0.10)	4.76 (0.08)	0.01 (–0.2; 4.59 to 4.92)[b]
120 minutes	4.88 (0.21)	5.44 (0.33)	0.01 (–0.56; 4.77 to 6.09)[b]
Required additional fentanyl intraoperatively, *n*	5	5	NR
Required additional fentanyl post surgery (CHEOPS >6), *n*	4	4	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

CHEOPS, Children's Hospital of Eastern Ontario Pain Score; NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Surgical procedures (*n*, group 1/group 2) were: herniotomy (9/3), urethroplasty (6/8), orchidopexy (6/7), urethural fistula closure/cystoscopy (4/6), not reported (0/1)

Mean state entropy and response entropy values were higher in group 1 than group 2 throughout the procedure; however, the difference was statistically significant only at the moment the child awoke (pre awakening) ($p = 0.03$) and at 1 minute post awakening ($p = 0.01$)

Methodological comments

Allocation to treatment groups: allocation to groups was according to computer-generated random numbers in a sealed envelope (not stated whether or not opaque)

Allocation concealment: an anaesthesiologist not involved in the anaesthetic management of the patient opened the envelope and either obscured or kept the entropy values visible on the monitor (not stated how data were obscured)

Blinding: stated only that the anaesthesiologist in group 2 was blinded to state and response entropy values (method of blinding not stated). Times to awakening and recovery were assessed by a resident anaesthesiologist who was blinded to the treatment allocation (i.e. unaware to which study group a patient belonged)

Analysis by ITT: stated that the data were analysed by intention to treat (data from all 50 randomised patients were analysed)

Comparability of treatment groups at baseline: age and weight were not statistically significantly different in the two groups. Group 2 included two girls, otherwise all participants were boys. Ethnicity was not reported. The surgical procedures performed, and the duration of surgery and anaesthesia were comparable between the two groups

Method of data analysis: Baseline data compared between study groups using chi-squared test or Wilcoxon rank-sum test as appropriate. Heart rate, mean arterial pressure, end-tidal isoflurane concentration, state entropy and response entropy were compared between groups over time using a generalised estimating equation as the observations were correlated

Sample size/power analysis: stated that a pilot study on 15 patients in a 'conventional' group gave a recovery time (assumed by reviewers to refer to time to awakening) of 7 ± 4 minutes. Anticipating a 5-minute difference in recovery time between the study groups, with an error of 0.05 and 90% power, a sample size of 15 in each group was calculated

Attrition/dropout: none reported (all patients included in analysis)

General comments

Generalisability: predominantly (88–100%) male; children of mean age 4–5 years (range 2–12 years); of presumably Indian ethnicity (not stated); with ASA health status grade I-II; undergoing lower abdominal or urological day care surgery with induction under i.v. propofol or inhaled sevoflurane, followed by maintenance under inhaled isoflurane. No specific risk factors for intraoperative awareness identified

Intercentre variability: NA (one centre)

Conflict of interests: stated none

NA, not applicable.

a Mean estimated from graph by reviewer (95% CI was reported but has not been extracted by the reviewer as it was not stated to which group(s) or difference the CI applies).

b As reported: CI does not include the stated mean difference (interpretation unclear).

Domain	Author's judgement (state: low/high/unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Computer-generated sequence
Allocation concealment	Unclear	Allocation sequence was in a sealed envelope but not reported whether or not envelope was opaque nor whom was responsible for entering the sequence from computer to envelope
Performance bias		
Blinding of participants and personnel	Unclear	No information on blinding of anaesthetists or patients was provided, except that anaesthetists were blinded to entropy values in group 2, which would not have concealed intervention assignment
Detection bias		
Blinding of outcome assessment	Low	Times to awakening and recovery were assessed by a resident anaesthesiologist who was blinded to the treatment allocation. Method of blinding not reported. Not stated whether or not assessment of other outcomes was blinded
Attrition bias		
Incomplete outcome data	Low	Analysis by ITT with no discernible attrition
Reporting bias		
Selective reporting	Low	No evidence to suggest selective reporting

Reviewer 1: GF Reviewer 2: JB

Reference and design	Technology	Participants	Outcome measures
Author: Vakkuri *et al*.[57] **Year:** 2005 **Study design:** RCT **Number of centres:** six **Countries:** Finland (three), Sweden (two), Norway (one) **Sponsor:** technical assistance, financial support, and equipment for data collection and analysis for this study were provided by Datex-Ohmeda, Helsinki, Finland	**Group 1:** E-Entropy and haemodynamic parameters (Entropy module of S/5 Anaesthesia Monitor with S/5 Collect software [GE Healthcare (formerly Datex-Ohmeda), Helsinki, Finland] Target device/index value: State entropy between 45 and 65 until last 15 minutes of anaesthesia then ideally 65 (not exceeding 70) during last 15 minutes. Response–state entropy difference (response entropy–state entropy) < 10. Heart rate and blood pressure to be kept within ± 20% of baseline (preoperative visit) values Commencement of monitoring: in operating room while patient was awake, before induction of anaesthesia **Group 2:** control: haemodynamic parameters only (heart rate and blood pressure to be kept within ± 20% of baseline values; entropy values recorded on a laptop computer but not displayed) Length of experience/ training of anaesthetist: anaesthetists were allowed to accustom themselves to the use of entropy monitoring for 3 weeks. All participants in the current study had substantial previous experience with electroencephalogram-based depth of anaesthesia monitors	**Total numbers involved:** 335 randomised (number randomised per group not reported). Numbers after attrition: group 1, 160; group 2, 160 Premedication used: oral diazepam 0.1–0.5 mg/kg 60 minutes before induction, except at Norwegian study site (where no premedication was used) General anaesthetic used: Induction: alfentanil bolus ≤ 30 µg/kg and propofol bolus 1.0–2.5 mg/kg Maintenance: continuous infusions of alfentanil ≤ 30 µg/kg/hour and propofol ≤ 9 mg/kg/hour. Lungs were normoventilated with a mixture of O_2 (35–50%) and N_2O (50–65%). In group 1, propofol was titrated to maintain the target state entropy; alfentanil or propofol boluses were permitted if state entropy suddenly increased; and alfentanil infusion was adjusted if the response entropy–state entropy difference > 10 or if haemodynamic parameters exceeded ± 20% of baseline values. In group 2, propofol and alfentanil were given to maintain heart rate and blood pressure within ± 20% of baseline values; propofol and alfentanil infusions were also adjusted depending on signs of unnecessarily deep or inadequate anaesthesia Recovery: infusions were closed down and N_2O was discontinued after skin closure Regional anaesthesia used: NR (implied that patients who underwent shoulder operations may have received inter-scalene plexus blocks post operatively) Muscle relaxants used: according to the anaesthetist's choice, when considered appropriate Antinausea drugs used: none reported Type of surgery: different types of gynaecological, abdominal, urological, orthopaedic, breast, thyroid and inguinal hernia operations Duration of surgery: NR Duration of GA (minutes) mean ± SD: group 1, 106 ± 48; group 2, 107 ± 49; difference NS	**Primary (powered) outcome:** • Time to awakening **Secondary outcomes:** • Device values • Anaesthetic consumption • Other drugs consumed (during surgery and in the PACU) • Durations of anaesthesia and surgery • Intraoperative reactions (movements, coughing, grimacing, eye opening) • Haemodynamic parameters (hypotension, hypertension, bradycardia, tachycardia) • Recovery times (to spontaneous breathing and extubation, eye opening, squeezing of the anaesthesiologist's hand on command, and orientation to time and place) • Time of discharge from operating room to PACU • Postoperative pain • Postoperative nausea and vomiting • Intraoperative awareness • Nurse estimation of postoperative variables (time needed in PACU, patient's need for care, patient's general recovery, patient's satisfaction with the anaesthesia, and actual time spent in the PACU) **Length of follow-up:** longest follow up appears to be the first postoperative day (for intraoperative awareness assessment) **Methods of assessing outcomes:** time to awakening: defined as the time to response to a verbal command Time to orientation to time and place: method of assessment not reported Anaesthetic consumption: infusion rates of anaesthetics were noted manually in the anaesthetic record Drug consumption: noted manually in the anaesthetic record

Reviewer 1: GF Reviewer 2: JB

Reference and design	Technology	Participants	Outcome measures
		Inclusion criteria: either sex; age 18–80 years; ASA physical status I, II or III; ability to read and understand the consent form; elective surgery procedures expected to last 45–150 minutes **Exclusion criteria:** known psychiatric or neurological disorders; history of major head injury; substance abuse; medication affecting the central nervous system; acquired scalp or skull abnormalities; uncontrolled hypertension (baseline systolic pressure >160 mmHg or baseline diastolic pressure >105 mmHg); baseline systolic blood pressure <90 mmHg; baseline heart rate <55 beats/minute; insulin-dependent diabetes; renal or hepatic disease; pregnancy; BMI >33 kg/m^2; any serious medical condition that would interfere with cardiovascular response assessment; cardiac, vascular or cranial neurosurgery; intraoperatively activated epidural analgesia; emergency or other non-elective surgery Baseline measurements (reported only for analysed population after attrition; $N = 320$); all differences stated NS: Sex (male), *n* (%): group 1, 44 (28); group 2, 39 (24) Age, years, mean ± SD: group 1, 45 ± 14; group 2, 47 ± 13 Ethnic groups, *n* (%): NR Weight (kg) mean ± SD: group 1, 71 ± 12; group 2, 71 ± 12 ASA grade I/II/III (*n*): group 1, 113/42/5; group 2, 101/57/2 Risk factors for awareness: stated none Comorbidities: none reported (note extensive exclusion criteria for comorbid patients) **Losses to follow-up:** reported with reasons but not separable by study group **Place of anaesthetic administration:** operating room	Pain scores: measured with a VAS (no details given) Nausea and vomiting: measured with a VAS 'on the day after anaesthesia was studied' (meaning seems ambiguous); no details of the VAS given) Intraoperative awareness: assessed by modified Brice interview (reference cited) first in the PACU and again during the first postoperative day

NR, not reported; NS, not statistically significant.

Outcome	Group 1	Group 2	*p*-value
Intraoperative awareness/recall	0	0	NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time (minutes) to emergence from anaesthesia			
Time to spontaneous breathing, median (range)	4.74 (0.00–18.0)	7.07 (–1.00–28.5)	<0.001
Time to eyes open, median (range)	6.08 (0.15–37.5)	10.8 (2.23–43.2)	<0.001
Time to squeezes hand on command, median (range)	8.60 (1.17–47.4)	12.7 (2.43–48.1)	<0.001
Time to orientation to time and place, median (range)	10.3 (1.17–48.7)	15.1 (4.08–113)	<0.001
Time (minutes) to extubation, median (range)	5.80 (3.00–27.3)	9.16 (1.67–32.3)	<0.001
Time (minutes) to discharge to/from the recovery room			
Time to discharge from operating room to PACU, median (range)	10.3 (3.83–42.4)	13.0 (5.00–49.8)	<0.001
Time to discharge from PACU, median (range)	134 (50–1293)	150 (7–1020)	0.21
Anaesthetic consumption[a]			
Propofol (mg/kg/minute), median (range)	0.10 (0.04–0.23)	0.11 (0.03–0.21)	<0.001
Alfentanil (μg/kg/minute), median (range)	0.60 (0.12–2.2)	0.57 (0.16–1.6)	0.54
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs			
Patient-reported VAS score	NR	NR	Stated no difference between groups
Pain/pain relieving drugs			
Patient-reported pain VAS score 1 day after anaesthesia	NR	NR	Both outcomes: stated no difference between groups
Opioid analgesic requirements in the PACU	NR	NR	
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Stated that the aim in all patients was to provide smooth, haemodynamically stable anaesthesia with the shortest possible emergence time and without intraoperative awareness

The initial eight to nine patients at each study site (total 50 patients) were assigned to a historical control group and their data were used to establish standard clinical practice of the participating anaesthetists before entropy monitoring started. The purpose of the historical control group was to get all of the study sites adjusted to the research protocol rather than to compare practices with and without central nervous system monitoring

Stated there were only minor differences between group 2 and the historical control group, with no differences statistically significant except higher values in the historical control group for: blood pressure at 1 minute after intubation ($p = 0.037$); propofol consumption during the last 15 minutes ($p = 0.001$); and alfentanil consumption during the last 15 minutes ($p = 0.02$)

Both group 1 and group 2 had more women than men because many of the participating centres included mainly gynaecological surgery patients in this study (patient numbers not reported by surgery type)

Stated that the incidence of untoward intraoperative reactions (movement or increased muscle tension, tearing, coughing, frowning, eye-opening, and episodes of hypertension, tachycardia or bradycardia) did not differ between study groups (no quantitative data reported)

Stated haemodynamic data were similar between groups; heart rates and blood pressures did not differ between groups until skin closure, where the entropy group had higher heart rate (mean $\pm$ SD: 63 ± 11 vs 60 ± 10 beats/minute; $p = 0.029$) and blood pressure (83 ± 10 vs 79 ± 12 mmHg; $p = 0.008$) (no other haemodynamic data reported)

Stated that recovery in the PACU was similar between groups. The incidence of postoperative nausea and vomiting, the nurse's estimation of time needed in the PACU, the nurse's estimation of the patient's need for care, the nurse's estimation of the patient's general recovery, and the patient's satisfaction with the anaesthesia, and the actual time spent in the PACU were similar between the two study groups (no quantitative data reported)

Cumulative percentages of patients not responding to verbal command, not yet discharged from the PACU, and not oriented to time and place after anaesthesia as a function of time were presented graphically (data not extracted by reviewer). Each of these outcomes was significantly smaller in group 1 than in group 2 ($p < 0.001$)

Stated that similar haemodynamic profiles in group 1 and group 2 are to be expected because haemodynamic responses guided the alfentanil dose in the study protocol in both groups, not only in group 2

Methodological comments

Allocation to treatment groups: random assignment according to computer-generated random numbers

Allocation concealment: each study site was provided with a sufficient number of closed randomisation envelopes (not stated whether or not opaque). With sequential coding, the subjects were treated in blocks of 10 (five patients per group). The envelopes were opened in the operating room immediately before the induction of anaesthesia

Blinding: not reported, other than entropy values recorded for patients in group 2 were not displayed

Analysis by ITT: no; 15 patients excluded after randomisation were omitted from the analysis

Comparability of treatment groups at baseline: ethnicity was not reported but age, sex, weight, and ASA health status did not differ significantly between group 1 and group 2. Height (data not extracted) also did not differ significantly between groups. (Note that baseline data were reported only for patients included in the analysis, not the full randomised population)

Method of data analysis: data normality was tested by Kolmogorov–Smirnov test and visual estimation of histograms. Unpaired *t*-test was used to test differences in haemodynamic variables, age, weight, height and the duration of anaesthesia. Mann–Whitney *U*-test was used to test differences in all other variables. Kaplan–Meier analysis was performed to test differences in cumulative recovery as a function of time after anaesthesia

Sample size/power analysis: sample size estimate was based a priori on time to awakening after propofol anaesthesia in another study (which specifically focused on clonidine premedication effects on awakening time) (reference cited). A minimum of 147 patients in each group was calculated to detect a 20% difference in patients' responses to a verbal command with a power of 0.8 and an α of 0.05

Attrition/dropout: 385 patients were initially recruited, of which 50 were used as historical controls to determine pre-existing anaesthesia practice. Stated that 17/385 patients were excluded, of which two were from the historical control group. The remaining 335 patients were randomised. The final analysis was on 320 patients (160 per group), with 15 patients excluded after randomisation. Reasons for exclusion were reported [most exclusions (14/17) were a result of 'lack of registered data'] but the origin of the excluded patients (historical control group, group 1 or group 2 was not reported)

General comments

Generalisability: adult population (mean age mid-40s), 72–76% female, assumed Scandinavian, with ASA health status predominantly I/II, undergoing varied types of surgery under inhaled GA with alfentanil and propofol. Population noted not to be at particular risk of intraoperative awareness

Intercentre variability: not reported. Stated that there may have been differences in the recovery protocols between study sites but the study protocol did not override the hospital policy for discharge from PACU to ward

Conflict of interests: study supported by the device manufacturer (formerly Datex-Ohmeda, then GE Healthcare, Finland); authors included a research engineer, research scientist and chief scientist of GE Healthcare and two medical advisors to GE Healthcare. One author was an employee of VTT Information Technology, Finland

a Reported that for propofol the significant difference ($p < 0.001$) applied both during the whole operation and especially during the last 15 minutes, but not stated to which of these time periods the numeric data refer.

Domain	Author's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Computer-generated random assignment
Allocation concealment	Unclear	Steps were taken to conceal allocation using envelopes that were opened only in the operating room immediately before anaesthesia. However, it was not stated whether envelopes were opaque or how codes were transferred from computer to envelopes
Performance bias		
Blinding of participants and personnel	Unclear	No information on blinding of anaesthetists or patients was provided, except that anaesthetists were blinded to entropy values in group 2, which would not have concealed intervention assignment
Detection bias		
Blinding of outcome assessment	Unclear	No information provided
Attrition bias		
Incomplete outcome data	Unclear	Attrition numbers and reasons reported but not separately by study group. Analysis was conducted only on the population after attrition (number randomised per group not discernible)
Reporting bias		
Selective reporting	Unclear	For several outcomes only a brief narrative statement that there was no difference between groups was provided, without any quantitative data or indication of variability
Other bias		
Other sources of bias	High	Notable conflict of interests discernible

Reviewer 1: JB **Reviewer 2: GF**

Reference and design	Technology	Participants	Outcome measures
Author: Wu *et al.*[58] **Year:** 2008 **Study design:** RCT **Number of centres:** one **Country:** Taiwan **Sponsor:** supported in part by the National Science Council	**Group 1:** E-Entropy response entropy and state entropy values shown on GE Datex-Ohmeda S/5™ Anaesthesia Monitor Target device/index value: response entropy and state entropy target values 35–45, corresponding to stable 2% EtSevo in the absence of major surgical stimulation. Gradient between response entropy and state entropy within 5–10. Anaesthesia monitored by entropy unless haemodynamic changes of 30% persisted for more than 5 minutes **Group 2:** conventional group using haemodynamic variables and physical signs (sweating, lacrimation, flushing, wrinkling of frontal facial muscles). If mean arterial pressure or heart rate fluctuated more than 30% of baseline value, EtSevo adjusted in steps of 0.2% until fluctuation < 30% Commencement of monitoring: in the operation room (appears to be before induction, although not explicitly stated so) Length of experience/ training of anaesthetist: NR	**Total numbers involved:** 68 patients enrolled and randomised; data for 65; group 1 = 34; group 2 = 31 Premedication used: none reported General anaesthetic used: Sevoflurane as sole inhalational anaesthetic Induction: fentanyl 2 µg/kg, propofol 2 mg/kg and 2 ml of 2% lidocaine Maintenance: after intubation sevoflurane delivered in a mixed flow of 0.3 l/minute air and 0.7 l/minute oxygen throughout operative period In maintenance period end-tidal CO_2 was kept between 35 and 40 mmHg Sevoflurane turned off once surgeon started to close skin layer Regional anaesthesia used: none used Analgesia used: fentanyl as above Muscle relaxants used: 0.30 mg/kg cis-atracurium Antinausea drugs used: NR Other drugs used: hypertension treated with nicardipine 0.25 mg (heart rate < 90/minute) or labetolol 2.5 mg (heart rate > 90/minute). Ephedrine 4 mg to treat hypotension (MAP < 70% of baseline). Atropine 0.5 mg i.v. bolus for bradycardia (heart rate < 45/minute) Type of surgery: total knee replacement Duration of surgery: approximately 1.5 hours Duration of GA (minutes) mean ± SD: group 1 = 133.74 ± 30; group 2 = 144.84 ± 30 **Inclusion criteria:** ASA I or II scheduled to undergo total knee replacement **Exclusion criteria:** history of cerebrovascular disease, treatment with psychoactive medication, existing cardiac dysrhythmia or weight < 70% or > 130% of ideal body weight **Baseline measurements:** Sex (male), *n* (%): group 1 = 28 (82%); group 2 = 25 (81%) Age (years), mean (SD): group 1 = 68.03 (6.1); group 2 = 68.90 (6.5) Ethnic groups, *n* (%): NR Weight (kg). mean (SD): group 1 = 64.8 (10.2); group 2 = 65.5 (12) ASA grade I/II: group 1 = 11/23; group 2 = 8/23 Risk factors for awareness: NR **Losses to follow-up:** reported with reasons, group 1 = 0, group 2 = 3 **Place of anaesthetic administration:** operation room	**Primary outcome:** • Consumption of sevoflurane **Secondary outcomes:** • Tourniquet-induced hyperdynamic responses • Pain status in the PACU • Postoperative nausea and vomiting • Level of awareness • Subjective complaints • Postoperative analgesic needs • Device values • Haemodynamic parameters **Length of follow-up:** 72 hours postoperatively for postoperative nausea and vomiting (follow-up for level of awareness and other outcomes unclear) **Methods of assessing outcomes:** consumption of sevoflurane determined by GE Datex Ohemeda S/5™ Anaesthetic Delivery Unit System Physiological changes at five major events recorded: intubation, tourniquet inflation, skin incision, tourniquet deflation, extubation For each event data collected at following time points: prior to commencement of event; 1 minute into event; 3 and 5 minutes into event Method of assessing level of awareness not reported

EtSevo, end-expiratory concentration of sevoflurane; MAP, mean arterial pressure; NR, not reported.

Outcome	Group 1, Entropy ($n = 34$)	Group 2, Conventional ($n = 31$)	p-value
Intraoperative awareness/recall	All 65 patients had no explicit recollection of procedure		NR
Patient distress and sequelae resulting from perioperative awareness	NR	NR	
Time to emergence from anaesthesia	NR	NR	
Time to extubation	NR	NR	
Time to discharge to/from the recovery room	NR	NR	
Anaesthetic consumption (ml), sevoflurane, mean (SD)	27.79 (7.4)	31.42 (6.9)	$p = 0.023$
HRQoL	NR	NR	
Nausea/vomiting/antisickness drugs			
Postoperative nausea and vomiting	No statistically significant difference between groups		NR
Pain/pain-relieving drugs			
Postoperative pain status and analgesic use	No statistically significant difference between groups		NR
Mortality	NR	NR	NR

NR, not reported.

Additional results/comments

No cardiovascular or cerebrovascular complication in any patient of either group postoperative

Height, hypertension diabetes reported for baseline but did not differ significantly between group 1 and group 2; same for heart rate and MAP

Treatment for hypertension, mean (SD): group 1 = 0.94 (1.15), group 2 = 1.48 (1.41), $p = 0.043$

Treatment for hypertension 45–60 minutes after tourniquet inflation: group 1 = 1, group 2 = 7, $p = 0.012$

Treatment for hypotension and bradycardia, no statistically significant difference between groups

Methodological comments

Allocation to treatment groups: randomised (no details)

Allocation concealment: no details reported

Blinding: study described as single blind but no details

Analysis by ITT: no (not all randomised patients analysed)

Comparability of treatment groups at baseline: stated no statistically significant differences in age, sex, ASA physical status, height, and weight

Method of data analysis: for nominal data, statistical analysis performed using chi-squared test. Age, sex, weight, height, duration of anaesthesia, heart rate, mean arterial pressure, consumption of sevoflurane statistically compared using independent sample *t*-test. RE and SE values were compared using Mann–Whitney *U*-test. Incidence of treatment of intraoperative adverse events (hypertension, hypotension, bradycardia) compared using Wilcoxon's ranked-sum test. A *p-value* <0.05 was considered significant

Sample size/power analysis: NR

Attrition/dropout: three patients from group 2 not included in results because of missing data (reasons not stated)

General comments

Generalisability: opioids only briefly given during induction phase but not sustained during the operative period. This approach might result in a higher incidence of increased blood pressure in both groups compared with other studies. The ranges of RE and SE were set arbitrarily and different results in consumption of sevoflurane, intraoperative haemodynamics and need for antihypertensive drugs could result with other entropy values. Results applicable to Chinese elderly adults, ASA status I/II undergoing total knee replacement surgery with sevoflurane anaesthesia with the stated entropy values. No specific risk factors for intraoperative awareness identified

Intercentre variability: NA, assumed single centre

Conflict of interests: NR

MAP, mean arterial pressure; NA, not applicable; NR, not reported.

Domain	Reviewer's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation.	Unclear	No methods described
Allocation concealment	Unclear	No methods described
Performance bias		
Blinding of participants and personnel	Unclear	Single blind (no details)
Detection bias		
Blinding of outcome assessment	Unclear	No details
Attrition bias		
Incomplete outcome data	Unclear	Three patients from group 2 excluded from analysis, reasons not stated
Reporting bias		
Selective reporting	Low	No evidence of selective reporting (but some results reported narratively only)

Reviewer 1: GF Reviewer 2: JS

Reference and design	Technology	Participants	Outcome measures
Author: Zhang *et al.*[40] **Year:** 2011 (enrolment November 2008–November 2010) **Study design:** RCT **Number of centres:** 13 **Country:** China **Sponsor:** NR (device manufacturer provided BIS electrodes)	**Group 1:** BIS-guided A-2000 BIS Monitor (Aspect Medical Systems, USA) Target device/ index value: 40–60 **Group 2:** routine TIVA (no details – possible variation among centres) BIS monitored but screen covered Commencement of monitoring: NR Length of experience/ training of anaesthetist: NR	**Total numbers involved:** number randomised not reported. Stated 5309 provided outcome data but only 5228 were analysed (group 1 = 2919; group 2 = 2309) Premedication used: none used General anaesthetic used: Induction: midazolam and propofol (doses at the discretion of the anaesthetist) Maintenance: propofol (dose at the discretion of the anaesthetist) Regional anaesthesia used: NR Analgesia used: drugs and doses at the discretion of the anaesthetist Muscle relaxants used: drugs and doses at the discretion of the anaesthetist Antinausea drugs used: NR Other drugs used: NR Type of surgery, group 1/group 2, (%): chest and abdominal 42.8/35.3; craniofacial and cervical 27.2/32.8; gynaecological and obstetric 14.1/12.5; neurosurgery 0.9/0.8; urinary 7.5/8.3; spine and limb (orthopaedic) 5.2/7.8; cardiac 0.8/0.9; other 1.3/1.4; overall difference between groups in surgery type: $p < 0.01$ Duration of surgery (≤1 hour/1–2 hours/>2 hours) (%): group 1: 18.7/43.4/37.9; group 2, 16.3/44.2/39.5; $p = 0.083$ Duration of GA: NR **Inclusion criteria:** age ≥18 years; without any apparent mental defect; scheduled for TIVA; and gave informed consent **Exclusion criteria:** patients unable to be interviewed after surgery (decision criteria not stated); unable to communicate in Mandarin Chinese; under awake intubation; or undergoing intraoperative arousal test **Baseline measurements:** Sex (male), *n* (%): group 1, 1237 (42.8);[a] group 2, 971 (42.6); $p = 0.902$ Age, mean ± SD, years: group 1, 46.95 ± 14.86; group 2, 46.06 ± 14.59; $p = 0.054$ Ethnic groups, *n* (%): NR; assumed majority were Chinese Weight, mean ± SD, kg: group 1, 63.80 ± 11.21; group 2, 63.39 ± 14.59; $p = 0.113$ ASA grade (1/2/>3),%:[b] group 1, 52.3/42.5/5.2; group 2, 59.5/37.5/2.9; $p < 0.01$ Risk factors for awareness: none reported; mentioned in discussion that the types of surgery that could influence awareness risk (cardiac, obstetric) did not differ between the study groups. Mentioned in the introduction that TIVA patients are at increased risk of awareness Comorbidities: NR	**Primary outcome:** • Intraoperative awareness **Secondary outcome:** • None reported **Length of follow-up:** 1 day and 4 days post surgery (awareness) **Methods of assessing outcomes:** awareness was assessed by a blinded observer using a structured questionnaire based on the Brice Interview on the first and fourth days post surgery. The research staff classified awareness as no awareness, possible awareness or awareness (criteria specified). An independent committee assessed the interview results and identified confirmed or possible awareness cases (committee membership not reported)

Reviewer 1: GF Reviewer 2: JS			
Reference and design	**Technology**	**Participants**	**Outcome measures**
		Losses to follow-up: of 5309 patients who provided outcome data, 81 (1.5%) were excluded from analysis (reasons reported, but not in all cases separately by study group). Unclear whether or not 5309 was the total number randomised **Place of anaesthetic administration:** NR	

NA, not reported; TIVA, total intravenous anaesthesia.

Outcome	Group 1	Group 2	*p*-value; OR (95% CI)
Intraoperative awareness/recall, *n* (%)			
Confirmed awareness	4/2919 (0.14)	15/2309 (0.65)	0.002; OR 0.21 (0.07 to 0.63)
Possible awareness	4/2919 (0.14)	6/2309 (0.26)	0.485
Confirmed or possible awareness	8/2919 (0.27)	21/2309 (0.9)	<0.01
Patient distress and sequelae resulting from perioperative awareness	NR	NR	NR
Time to emergence from anaesthesia	NR	NR	NR
Time to extubation	NR	NR	NR
Time to discharge to/from the recovery room	NR	NR	NR
Anaesthetic consumption	NR	NR	NR
HRQoL	NR	NR	NR
Nausea/vomiting/antisickness drugs	NR	NR	NR
Pain/pain-relieving drugs	NR	NR	NR
Other morbidity (e.g. cognitive dysfunction)	NR	NR	NR
Mortality	NR	NR	NR

NR, not reported.

Additional results/comments (e.g. early response factors, QoL)

Anaesthesia history differed significantly between study groups at baseline ($p = 0.017$). The proportion with anaesthesia history was 18.1% in group 1 and 15.5% in group 2

BIS values were obtained for only six of the total 19 confirmed awareness cases (attributed to poor data collecting and recording). Of these, five cases showed light anaesthesia (BIS >60), with most (four) of these light anaesthesia cases occurring in group 2. BIS data from one patient with intraoperative awareness in group 1 indicated that BIS exceeded the target value (BIS>60 for 21 minutes, with a maximum BIS value of 75), giving light anaesthesia

Anaesthetic consumption was not specified as an outcome but the authors mention that intraoperative records showed that in some patients with awareness insufficient anaesthetic had been applied

Methodological comments

Allocation to treatment groups: carried out at each individual centre through computer-generated random numbers. Details not specified

Allocation concealment: NR

Blinding: anaesthetist was blinded to BIS values in group 2 (monitor screen was covered); stated that interviewers and patients were blinded to the group allocation (details not specified)

Analysis by ITT: not an ITT analysis: number randomised unclear and analyses excluded attrition

Comparability of treatment groups at baseline: the groups differed statistically significantly in terms of patients' ASA status (a higher proportion with worse grades in group 1); anaesthesia history (a higher proportion in group 1 had previous anaesthesia); and the type of surgery received (details above). These variables were tested in univariate analyses (details not specified) to exclude a confounding effect on intraoperative awareness ($p>0.05$). The groups were otherwise well balanced for age, weight, sex, type of airway (tracheal intubation or laryngeal mask), proportion with a difficult airway and proportion with stable/unstable circulation status

Method of data analysis: independent-samples *t*-tests for intergroup comparisons and also chi-squared tests (no other details given)

Sample size/power analysis: stated (without citing a source) that the required sample size in each group was from 2000 to 2800 to achieve 90% power at 5% two-sided type I error. To allow for missing data, 5000–6000 patients were recruited

Attrition/dropout: number randomised not reported. Stated that outcome data were collected from 5309 patients but only 5228 (i.e. 81 fewer) were analysed. Reasons for attrition were lack of information on group allocation ($n = 54$; not reported separately by group; stated that this attrition was without awareness cases); age <18 years ($n = 11$ in group 1; $n = 10$ in group 2); failure to participate in either of the postoperative interviews ($n = 2$ in group 1; $n = 2$ in group 2); postoperative death ($n = 1$; group not specified); and surgery cancelled after anaesthesia induction ($n = 1$; group not specified)

General comments

Generalisability: Chinese adult population receiving TIVA for a wide range of surgical procedures in 13 centres; no specific risk factors for intraoperative awareness identified

Intercentre variability: NR

Conflict of interests: device manufacturer (Aspect Medical Systems) provided BIS electrodes

NR, not reported.

a Reported percentage differs slightly from actual value (<1%).

b The reported percentages imply that the data are based on fewer patients than were allocated to the study groups (approximately 2650–2654 patients in group 1 and approximately 2224–2241 patients in group 2) (back-calculated numbers are approximate because of rounding errors).

Domain	Reviewer's judgement (state: low/high/ unclear risk)	Support for judgement
Selection bias		
Random sequence generation	Low	Computer-generated random numbers
Allocation concealment	Unclear	No information provided
Performance bias		
Blinding of participants and personnel	Low	Stated that anaesthetists and patients were blinded to group allocation
Detection bias		
Blinding of outcome assessment	Low	Stated that interviewers were blinded to group allocation
Attrition bias		
Incomplete outcome data	Unclear	Attrition not included in analysis; not an ITT analysis; attrition incompletely reported and unclear whether or not balanced across groups
Reporting bias		
Selective reporting	Low	Study focused on one outcome (awareness)