Bispectral index for improving anaesthetic delivery and postoperative recovery (Review)

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[Intervention Review]

Bispectral index for improving anaesthetic delivery and postoperative recovery

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ABSTRACT

Background

The use of clinical signs may not be reliable to measure the hypnotic component of anaesthesia. The use of bispectral index to guide the dose of anaesthetics may have certain advantages over clinical signs.

Objectives

The objective of this review was to assess whether bispectral index (BIS) reduced anaesthetic use, recovery times, recall awareness and cost.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 2), MEDLINE (1990 to May 2007), EMBASE (1990 to May 2007) and reference lists of articles.

Selection criteria

We included randomized controlled trials comparing BIS with clinical signs (CS) in titrating anaesthetic agents.

Data collection and analysis

Two authors independently assessed trial quality, extracted data and analysed the data. We contacted study authors for further details.

Main results

We included 20 studies with 4056 participants. Seven recent trials are still awaiting assessment. BIS-guided anaesthesia reduced the requirement for propofol by 1.30 mg/kg/hr (578 participants; 95% confidence interval (CI) -1.97 to -0.62) and for volatile anaesthetics (desflurane, sevoflurane, isoflurane) by 0.17 minimal alveolar concentration equivalents (MAC) (689 participants; 95% CI -0.27 to -0.07). Irrespective of the anaesthetic, BIS reduced the recovery times: time for eye opening by 2.43 min (996 participants; 95% CI -3.60 to -1.27), response to verbal command by 2.28 min (717 participants; 95% CI -3.47 to -1.09), time to extubation by 3.05 min (1057 participants; 95% CI -3.98 to -2.11) and orientation by 2.46 min (316 participants; 95% CI -3.21 to -1.71). BIS shortened the duration of postanaesthesia care unit stay by 6.83 min (584 participants; 95% CI -12.08 to -1.58) but did not reduce time to home readiness (329 participants; 95% CI -30.11 to 16.09). The BIS-guided anaesthesia significantly reduced the incidence of intraoperative recall awareness in surgical patients with high risk of awareness (OR 0.20, 95% CI 0.05 to 0.79).

Authors' conclusions

Anaesthesia guided by BIS within the recommended range (40 to 60) could improve anaesthetic delivery and postoperative recovery from relatively deep anaesthesia. In addition, BIS-guided anaesthesia has a significant impact on reduction of the incidence of intraoperative recall in surgical patients with high risk of awareness.

PLAIN LANGUAGE SUMMARY

Bispectral index for improving anaesthetic delivery and postoperative recovery

Bispectral index has been shown to improve both anaesthetic delivery and postoperative recovery and to reduce the incidence of intraoperative recall awareness. The use of clinical signs, such as blood pressure and heart rate, for guiding doses of anaesthetic can result in either an overdosage or underdosage of anaesthetic agents. Bispectral index (BIS) is a scale derived from cerebral electrical activity to measure the effect of specific anaesthetic drugs on the brain. It may be useful to tailor doses of anaesthetic to achieve adequate depth of anaesthesia. This review of 20 trials found that anaesthesia guided by BIS, to keep it within the recommended range (40 to 60), could decrease the consumption of anaesthetic drugs and enhance recovery from relatively deep anaesthesia. Moreover, BIS could reduce the incidence of perioperative recall in surgical patients with high risk of awareness.

BACKGROUND

At present, the practice of anaesthesia is based on the concept of components of anaesthesia resulting from separate pharmacological actions of multiple agent administration (Kissin 1997). Many anaesthesiologists rely on somatic signs (motor responses, changes in respiratory pattern) and autonomic signs (tachycardia, hypertension, lacrimation, sweating) to guide the dosage of anaesthetic agents in order to achieve the basic goals of anaesthetic management, that is unconsciousness (hypnotic effects), blockade of somatic motor responses and suppression of autonomic responses to noxious stimulation. However, these clinical signs are not reliable measures of the conscious state of anaesthetized patients (Mahla 1997). The use of these clinical signs in judging dosage of anaesthetic agents can lead to either over dosage or under dosage, which can result in adverse effects due to too deep or too light anaesthesia.

Bispectral index (BIS), weighted values derived from a historical database of encephalography of anaesthetized patients, has been introduced into clinical practice to measure the hypnotic component of anaesthesia (Glass 1997; Kissin 2000; Rampil 1998). It was suggested that using BIS to guide anaesthetic administration would allow optimization of drug delivery to the needs of individual patients in order to avoid unnecessarily deep or too light anaesthesia due to over dosage or under dosage of the hypnotic medications (Sebel 2001). Several studies were conducted to assess the effect of BIS monitoring on the utilization of currently available anaesthetic agents, such as propofol, desflurane and sevoflurane (Gan 1997; Johansen 1998; Nelskyla 2001; Song 1997; Song 1998). There was a survey among anaesthesiologists regarding the routine use of BIS monitoring in anaesthesia (Johansen 1998). Although the majority of the respondents found that the monitor was easy to use, and it provided useful information, their comments revealed some ambivalence towards hypnotic titration using a BIS monitor. Most respondents felt that no changes occurred in their individual drug usage. Some respondents who reported a change in their practice felt that the hypnotic medication use might decrease whilst analgesic and haemodynamic control agent use might increase. A previous study by Song et al (Song 1997) reported increased use of mivacurium in the BIS-targeted group.

To determine the impact of electroencephalogram (EEG) bispectral index monitoring on drug usage and recovery during ambulatory anaesthesia, Badrinath et al (Badrinath 1999) conducted a historical control study and reported an increase in the use of intra-operative opioids in the BIS-guided group. The increased use of either a muscle relaxant or an opioid might relate to the ability to maintain 'lighter' planes of anaesthesia with BIS.Thus, the impact of BIS monitoring on drug usage in routine clinical practice remains to be confirmed. Furthermore, it was postulated that the optimization of the level of anaesthesia by BIS might have an impact on the incidence of intraoperative recall aware-

ness.However, because of the low incidence of preoperative recall awareness, an extremely large number of patients would be needed (O'Connor 2001). Moreover, the decreased anaesthetic consumption and enhanced recovery by BIS-guided anaesthesia has to be weighed against the cost of BIS monitoring (Paventi 2001; Yli-Hankala 1999).

Since 1977, several articles and abstracts regarding the utility of BIS have been published from numerous medical research and academic institutions. It has been suggested that close titration of anaesthetic effect with the BIS monitor may improve some measures of patient outcome and operating suite efficiency. Questions regarding the utility of BIS are equally valuable for the clinical practice of anaesthesia and are focused on in this systematic review.

OBJECTIVES

The primary objective in this review focused on whether the incorporation of BIS into the standard practice of managing anaesthesia can reduce: consumption of anaesthetic agents, recovery time, incidence of recall awareness and total cost of anaesthesia management in surgical patients undergoing general anaesthesia at either low risk or high risk of recall awareness during the operation.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled or quasi-randomized controlled trials dealing with the use of BIS or clinical signs(CS) in the titration of anaesthetic agents regardless of blinding or the language of the article.

Types of participants

We included men and women aged over 18 years undergoing any type of surgery (including caesarean section) under general anaesthesia.

Types of interventions

We included studies, with at least two arms which:

1. used BIS to guide the dose of either an intravenous anaesthetic, hypnotic or volatile anaesthetic;
2. used the standard practice of the conventional criteria (e.g. the changes in a cardiovascular parameter, changes in respiratory patterns, lacrimation etc) based on the judgement of the attending anaesthesiologist to increase or decrease the anaesthetic drug delivery.

Types of outcome measures

We included continuous outcomes in the form of:

1. anaesthetic consumption or requirement for anaesthetics, titrated during anaesthesia;
2. amount of drugs (e.g. intravenous or inhalation anaesthetics, muscle relaxants, narcotic analgesics and other adjuvants) used during maintenance of anaesthesia;
3. the time needed to achieve the primary recovery end points, namely: response to command and orientation, extubation, eye opening, leaving the operating theatre and eligibility for discharge from the postanaesthesia care unit (PACU);
4. the cost (e.g. total cost during anaesthesia and PACU stay).

Dichotomous outcomes were in terms of intraoperative recall awareness.

Search methods for identification of studies

We searched the following sources for relevant trials:
The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2007, Issue 2), MEDLINE (1990 to May 2007), EMBASE (1990 to May 2007).
We identified randomized controlled trials (RCTs) using the search strategies found in Appendix 1 (MEDLINE Silver Platter), Appendix 2 (EMBASE Silver Platter), Appendix 3 (CENTRAL).
We searched the reference lists of retrieved trial reports and review articles for additional studies.
We did not impose any language restriction.

Data collection and analysis

We scanned the titles and abstracts of reports identified by the electronic searching for a list of possible relevant reports. Two authors (YP, NB) independently assessed all studies to be included. We resolved disagreements by a consensus meeting between the three authors (YP, NB and AP).

Quality assessment

We considered the method and adequacy of randomization, blinding of the study and description of withdrawals in the quality assessment. This was conducted independently by the two authors (YP and NB). We used a standardized quality assessment checklist.
.
The allocation concealment was considered as:
A. (adequate) when the allocation concealment was described as using central randomization or sequentially numbered, sealed opaque envelopes;

B. (uncertain) when studies did not report any concealment approach;
C. (inadequate) when the allocation was described as alternation, the use of case record numbers, date of birth or day of the week and open list of random numbers; and
D. when allocation concealment was not used.
We resolved disagreements by a consensus meeting between the three authors (YP, NB and AP).

Data extraction

We included all relevant information on the included studies in a data extraction form. This included details of study method; country of investigation; number of patients; demographic characteristics; treatment groups; types of surgery; details of anaesthesia management; experience of the anaesthesiologists; BIS values during maintenance and at the end of surgery; and any other relevant outcomes. We extrapolated data from figures as needed.

Data analysis

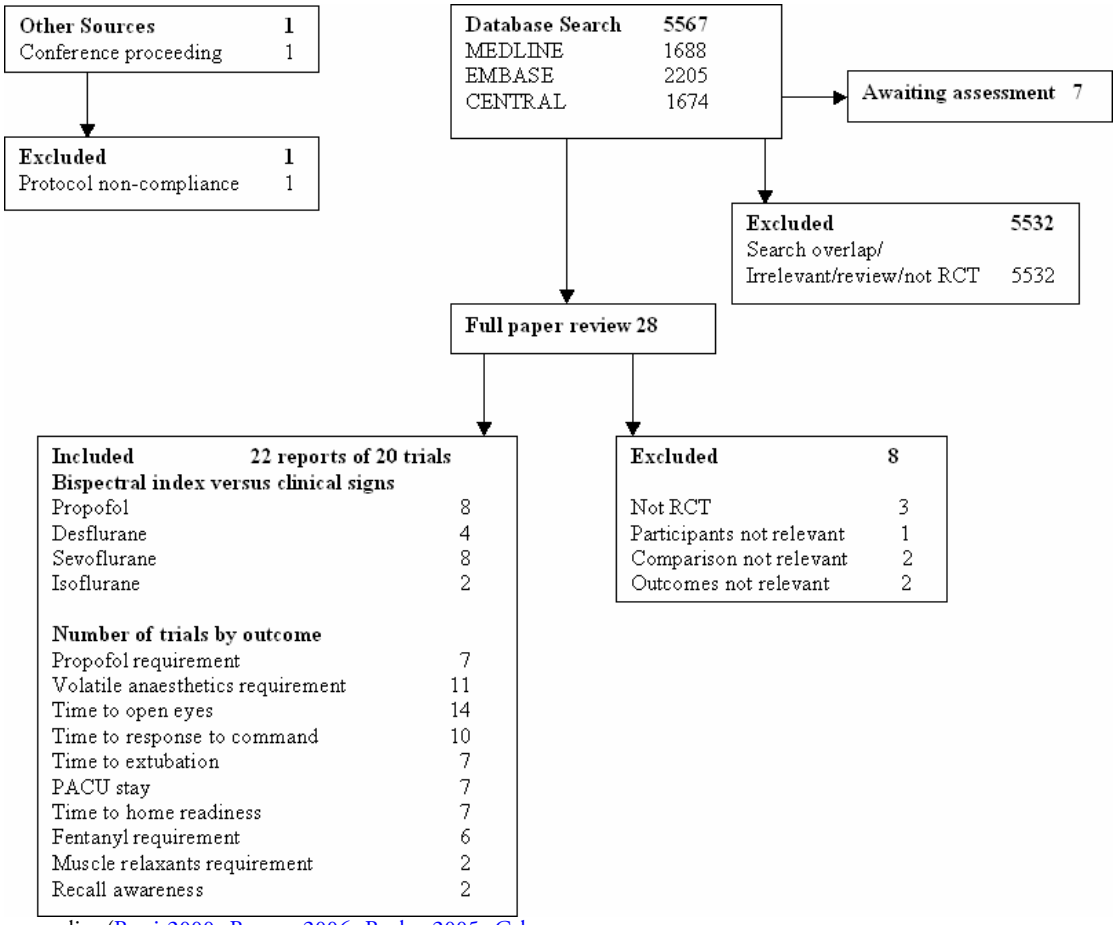
We examined the included studies for methodological and clinical heterogeneity. We used the Cochrane Collaboration statistic package Meta View in Review Manager (RevMan 4.2), to analyse the data. We summarized the outcomes separately based on types of anaesthetic agent, i.e. propofol and volatile anaesthetics (desflurane, isoflurane and sevoflurane).
In order to determine the overall effect of the BIS on the requirements for volatile anaesthetics, we converted the end tidal concentrations of volatile anaesthetics into minimal alveolar concentration (MAC) equivalents. (MAC is the alveolar concentration of an anaesthetic at 1 ATM (1 ATM = 760 mm Hg) that prevents movement in response to surgical stimuli in 50% of patients). The MACs of desflurane, sevoflurane and isoflurane are 6.0, 1.8 and 1.15 for people of ages 30 to 60 years and 5.17, 1.45 and 1.0 for people older than 65 years respectively) (Myles 2004). For studies that reported the use of volatile anaesthetics in MAC hours, for example in Luginbuhl 2003, we divided this value by the duration of anaesthesia.
To determine the overall effect of the BIS on requirements of propofol, we calculated the weighed mean difference of the infusion rate of propofol (mg/kg/hr, milligramme per kilogramme per hour) (see table of 'Comparison and data 01.01'). We converted the reports in studies using units of μg/kg/hr to mg/kg/hr.
If there was statistical evidence of heterogeneity ($I^2 > 50\%$), we applied the random-effects model. In addition, for studies reporting medians and ranges or interquartile ranges, we used the medians as the means and made a pooled estimate of the standard deviation (SD) from the studies that reported it. We used weighted mean difference (WMD) to demonstrate the effect measure for continuous variables having the same unit across the studies and standardized mean difference for variables with different scales of measurement. For binary outcomes such as the occurrence of recall awareness, we used the odds ratio (OR) to demonstrate the effect measure. We also performed sensitivity analyses to determine the effect of methodological quality on the results. We set the level of significance for all tests set at a P value of 0.05. We did not perform a sensitivity analysis for dropouts because the number of dropouts was small.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
From the initial search strategy we identified 5567 potential studies. From those studies, we identified 35 potentially relevant references and retrieved them for further assessment (see Additional Figure 1). We excluded eight references (Burrow 2001; Guignard 2001; Johansen 2000; Lehmann 2003; Pavlin 2001; Sebel 1997; Song 1998; Yli-Hankala 1999) for the reasons cited in tables 'Characteristics of excluded studies'.

Figure 1. Searching results 1990 to May 2007



Seven studies (Berti 2000; Boztug 2006; Bruhn 2005; Caba 2003; Kreuer 2005; Leslie 2005; Samarkandi 2007) are still awaiting assessment.

We included 20 studies (Ahmad 2003; Anez 2001; Assare 2002; Basar 2003; Gan 1997; Hachero 2001; Kreuer 2003; Luginbuhl 2003; Masuda 2002; Morimoto 2002; Myles 2004; Nelskyla 2001; Paventi 2001; Puri 2003; Recart 2003; Song 1997; Struys 2001;Tufano 2000; White 2004; Wong 2002) which fulfilled the inclusion criteria of comparing the use of BIS (BIS group) with clinical signs (CS group) in guiding doses of currently used anaesthetics (propofol, desflurane, sevoflurane or isoflurane) (see the table 'Characteristics of included studies'). Of these 20 studies, five studies were published in languages other than English: two in Japanese (Masuda 2002; Morimoto 2002); two in Spanish (Anez 2001; Hachero 2001) and one in Italian (Tufano 2000).

BIS was used to guide doses of propofol in eight studies (Anez 2001;Gan 1997;Hachero 2001; Kreuer 2003; Luginbuhl 2003; Masuda 2002; Luginbuhl 2003; Struys 2001); desflurane in four studies (Luginbuhl 2003; Recart 2003; Song 1997; White 2004); sevoflurane in eight studies (Ahmad 2003; Assare 2002; Basar 2003; Morimoto 2002; Nelskyla 2001; Paventi 2001; Song 1997; Tufano 2000) and isoflurane in two studies (Puri 2003; Wong 2002). Two studies (Myles 2004; Puri 2003) were conducted in patients with high risk of awareness during operation. Eleven studies (Ahmad 2003; Assare 2002; Anez 2001; Gan 1997; Kreuer 2003; Luginbuhl 2003; Morimoto 2002; Nelskyla 2001; Paventi 2001; Song 1997; White 2004) were conducted in ambulatory surgical patients.

There were three studies (Luginbuhl 2003; Song 1997; Tufano 2000) with four treatment groups. They were divided into two sub studies based on anaesthetics titrated by BIS or clinical signs .There were two studies (Kreuer 2003; White 2004) with three treatment arms. Only the arms using BIS and clinical signs were

taken into consideration for statistical analyses.

The BIS target values for guiding anaesthetic doses varied across studies. The target was a BIS value of 60 in two studies (Assare 2002; Song 1997); 50 to 60 in four studies (Ahmad 2003; Nelskyla 2001; White 2004; Wong 2002); 50 in two studies (Kreuer 2003; Struys 2001); 45 to 55 in three studies (Luginbuhl 2003; Puri 2003; Recart 2003); 45 to 60 in one study (Gan 1997) and 40 to 60 in seven studies (Anez 2001; Basar 2003; Hachero 2001; Masuda 2002; Morimoto 2002; Myles 2004; Paventi 2001).

There was inconsistency across studies in management of the signs of inadequate analgesia (hypertension and tachycardia) despite achieving target BIS values in the BIS group or target concentrations of anaesthetics in the clinical signs (CS) group (see Additional Table 1). Most of the included studies used incremental doses of narcotics, that is fentanyl (Hachero 2001; Luginbuhl 2003; Morimoto 2002; Recart 2003; Song 1997; White 2004; Wong 2002); sufentanil (Ahmad 2003); remifentanil (Kreuer 2003; Luginbuhl 2003; Paventi 2001; Struys 2001) and alfentanil (Gan 1997; Nelskyla 2001) for management of inadequate anaesthesia or analgesia. In Basar 2003, signs of inadequate anaesthesia or analgesia were managed by increasing the concentration of sevoflurane. White et al used esmolol to treat sustained increases in heart rate (White 2004). Antihypertensive agents or labetalol were added to treat or control haemodynamic responses in Gan 1997 and Wong 2002 (see Additional Table 1).

Table 1. Anaesthetic technique and strategy in management of inadequate analgesia

Study	Anaesthetic Tech.	Titrating strategies	Note
Ahmad 2003	Endotracheal GA. Induction: sevoflurane Maintenance: sevoflurane-sufentanil-nitrous oxide-a relaxant.	Sevoflurane/sufentanil titrated for increased blood pressure/heart rate > 20%, despite a BIS value of 50-60 or end tidal sevoflurane concentration 2%	GA = general anaesthesia
Anez 2001	LMA GA. Induction: propofol-alfentanil Maintenance: propofol-rocuronium	NA	LMA = laryngeal mask airway, NA = not available
Assare 2002	LMA GA. Induction:propofol-fentanyl Lidocaine infiltration prior to incision Maintenance: sevoflurane-nitrous oxide (no muscle relaxant)	NA	
Basar 2003	Endotracheal GA. Induction: fentanyl-thiopentone Intubation: rocuronium Maintenance: sevoflurane-nitrous	Inadequate analgesia in both groups managed by increased concentration of sevoflurane (no supplemental fentanyl)	

Table 1. Anaesthetic technique and strategy in management of inadequate analgesia (*Continued*)

	oxide		
Gan 1997	Endotracheal/LMA anaesthesia Induction: propofol alfentanil Maintenance: 50%nitrous in oxygen-propofol-alfentanil-relaxants	BIS group: increasing alfentanil if BIS was within the recommended range (45-60) SP group: increasing doses of either propofol, alfentanil or antihypertensive agents	
Hachero 2001	Endotracheal GA. Induction: propofol Intubation: mivacurium Maintenance:propofol-fentanyl-mivacurium	Signs of inadequate anaesthesia managed in both groups by fentanyl	
Kreuer 2003	Endotracheal GA. Induction: propofol-remifentanil Intubation: cisatracurium. Maintenance: propofol (TCI)- remifentanil (constant infusion)	Remifentanil infusion was given in both groups for signs of inadequate anaesthesia despite achieving propofol target concentration or a target value of 50 for BIS	TCI = target controlled infusion
Luginbuhl 2003	Endotracheal GA Induction: propofol and fentanyl. Intubation: vecuronium Maintenance: propofol-fentanyl or desflurane-fentanyl	BIS group: propofol or desflurane to keep BIS 45-55 and opioids according clinical criteria CS group: propofol or desflurane and opioids according to haemodynamic and vital sign criteria(within 20% of the baseline value	
Masuda 2002	Endotracheal GA Induction: propofol-fentanyl Intubation: vecuronium Maintenance: propofol-nitrous oxide - fentanyl-vecuronium	NA	
Morimoto 2002	Endotracheal GA Induction:thiopentone, Intubation: vecuronium Maintenance:sevoflurane-nitrous oxide- fentanyl-vecuronium	Managed by fentanyl 50 - 100 micrograms, despite 2% in sevoflurane in both groups.	
Myles 2004	Relaxant general anaesthesia. Induction: midazolam-propofol or thiopentone Intubation: nondepolarizing muscle relaxants. Maintenance: Propofol or volatiles-nitrous oxide-opioids. Hypnotic drugs .Combined general and regional anaesthesia	Narcotic analgesics on the discretion of the attending anaesthesiologists	

Table 1. Anaesthetic technique and strategy in management of inadequate analgesia (*Continued*)

Nelskyla 2001	Endotracheal GA. Induction:propofol Intubation: rocuronium Maintenance: Sevoflurane (0.94%-1.4%)-Nitrous oxide-rocuronium	Supplemental alfentanil given for haemodynamic variables>25% of the preanaesthetic value, despite BIS of 50-60 in BIS group or sevoflurane concentration of 1.4% in CP group	
Paventi 2002	Endotracheal GA. Induction: remifentanil -thiopentone Intubation: vecuronium Maintenance: sevoflurane-nitrous oxide-remifentanil-vecuronium.	Remifentanil infusion (0.4 microgram/kg/min) for both groups	
Puri 2003	Endotracheal GA. Induction: midazolam-morphine-thiopentone Intubation:vecuronium. Maintenance: isoflurane-nitrous oxide-morphine	Signs of inadequate analgesia (tachycardia, hypertension, sweating, lacrimation etc) in both groups managed by morphine before vasodilators or beta-blocker	
Recart 2003	Endotracheal GA Premedication: Induction: propofol-fentanyl Intubation: rocuronium Maintenance-desflurane-fentanyl	Intermittent intravenous fentanyl 0.5 mg/kg as needed to maintain haemodynamic variables within 15% of the baseline value Labetalol to control sympathetic responses as needed (in the presence of adequate hypnotic and analgesic states) Intermittent intravenous fentanyl 0.5 mg/kg as needed to maintain haemodynamic variables within 15% of the baseline value Labetalol to control sympathetic responses as needed (in the presence of adequate hypnotic and analgesic states)	
Song 1997	Endotracheal GA. Induction: fentanyl-propofol. Intubation:succinylcholine Maintenance: desflurane or sevoflurane-nitrous-fentanyl-mivacurium (at least 1-2 TOF)	Inadequate analgesia (haemodynamic variables>20%of baseline) managed by supplemental doses of fentanyl (25-30 microgram)	
Struys 2001	Endotracheal GA. Induction: remifentanil, propofol .Intubation: rocuronium. Maintenance: remifentanil infusion (0.5 micro gramme/kg/min)-propofol infusion	Remifentanil infusion	

Table 1. Anaesthetic technique and strategy in management of inadequate analgesia (*Continued*)

Tufano 2000	Endotracheal GA. Induction: Propofol. Intubation: Cisatracurium. Maintenance: propofol infusion or sevoflurane - nitrous oxide-cisatracurium-fentanyl	NA	
White 2004	Endotracheal GA .Induction: propofol and fentanyl Intubation:succinylcholine. Maintenance: desflurane-nitrous -cisatracurium	Esmolol to treat sustained increased heart rate	
Wong 2002	Endotracheal GA. Induction: propofol-fentanyl-midazolam Intubation : rocuronium. Maintenance : isoflurane-nitrous oxide-fentanyl-rocuronium-fentanyl	BIS group: BIS > 60 increasing isoflurane concentration; BIS = 50-60 giving supplemental fentanyl; BIS < 50 decreasing isoflurane concentration and supplementing fentanyl (signs of inadequate anaesthesia)or labetalol (no sign of inadequate anaesthesia)SP group: increasing isoflurane concentration or supplemental fentanyl or labetalol for management of hypertension(>25%) or tachycardia (>90 beats per minute).	

All but one study (Assare 2002) used nondepolarizing muscle relaxants either for endotracheal intubation or during maintenance of anaesthesia. Assare 2002 was the only study that was conducted in a short surgical procedure (arthroscopy) with duration less than 20 minutes and did not use any muscle relaxants, while the other studies were conducted in relatively longer surgical procedures with durations of longer than 30 minutes.

Only two studies mentioned the length of experiences of the anaesthesiologist, that is greater than one year (Basar 2003) and greater than five years (Wong 2002). The others did not give any information regarding the experience of the anaesthesiologists.

Risk of bias in included studies

Most of the included studies, with the exception of one (Anez 2001), were randomized controlled trials (RCTs). Anez 2001 was considered quasi-randomized because it used sequential randomization. Allocation concealment was classified as adequate (A) in four studies (Ahmad 2003; Gan 1997; Luginbuhl 2003; Myles 2004). Anez 2001 was categorized as class D because of its quasi-randomization. The other studies did not mention allocation concealment, therefore, we classified them as uncertain (grade B).

Anaesthesiologists could not be blinded to the assigned group, in all studies. Ten studies (Gan 1997; Hachero 2001; Kreuer 2003; Luginbuhl 2003; Myles 2004; Paventi 2001; Recart 2003; Tufano 2000; White 2004; Wong 2002) blinded the outcome assessors to the assigned group.

Four studies reported on patients excluded from analyses because of protocol violations (2/99 in Ahmad 2003; 28/268 in Gan 1997; 14/60 in Morimoto 2002 and 8/68 in Wong 2002). None of these studies mentioned intention-to-treat analysis.

Effects of interventions

Requirement of anaesthetics

There are some variations in the results across studies regarding the consumption of anaesthetics (see tables 'Comparison and data 01.01 and 01.02'). The combined result from seven studies involving 578 participants demonstrated the significant effect of BIS monitoring in reducing propofol consumption, with an overall

decrease of 1.30 mg/kg/hr (95% CI -1.97 to -0.62).
The results for anaesthetic consumption of individual volatile anaesthetics are summarized in the tables ('Comparison and data 01.02.01, 01.02.02,01.02.03'). The combined results from 11 studies with a total of 689 participants demonstrated the significant effect of BIS monitoring on reducing use of volatile anaesthetics including desflurane, isoflurane and sevoflurane, with an overall decrease of 0.17 MAC equivalents (95% CI -0.27 to -0.07).

Recovery profiles

Early recovery times were studied, described as time to eye opening, time to response to command, time to extubation and time to orientation (see the tables 'Comparison and data 02.01, 02.02, 02.03 and 02.04'). The overall effect of BIS was a reduction in early recovery times. The time to eye opening was reduced by 2.43 minutes (996 participants; 95% CI -3.60 to -1.27), the time for response to command was reduced by 2.28 minutes (717 participants; 95% CI -3.47 to -1.09), time to extubation was reduced by 3.05 minutes (1057 participants; 95% CI -3.98 to -2.11) and the time to orientation was reduced by 2.46 minutes (316 participants; 95% CI -3.21 to -1.71).

Postanaesthetic care unit (PACU) stay

The time of PACU stay is summarized in the table 'Comparison and data 02.05'. The combined result indicated a significant effect of BIS on the PACU stay with an overall reduction of 6.83 minutes (584 participants; 95% CI -12.08 to -1.58).

Time to home readiness (discharge time)

The time to home readiness is summarized in the table 'Comparison and data 02.06'. The combined result failed to demonstrate any effect of BIS in reduction of the time to home readiness, with the overall effect of -7.01 minutes (329 participants; 95% CI -30.11 to 16.09).

Requirement for narcotic analgesics

The table 'Comparison and data 03.01' shows the requirements for a narcotic analgesia (fentanyl) in nine studies. Only one study (Hachero 2001) reported a significantly increased use of fentanyl in the BIS group. The combined result indicated a non-significant increase in requirements for a narcotic analgesic in the BIS group, with an overall effect of 18.02 µg (276 participants, 95% CI -25.16 to 61.20).

Requirement for muscle relaxants

Only one study by Song et al (Song 1997) reported a significant increase in the use of mivacurium in the BIS group (see table 'Comparison and data 04.01'), while other studies did not show significantly increased requirements of other relaxants.

Incidence of intraoperative recall awareness

The table 'Comparison and data 05.01' shows the occurrence of awareness in two studies (Myles 2004; Puri 2003). These were conducted in surgical patients with high risk of awareness. The combined result indicated a significant reduction in the incidence of awareness in the BIS group, with an overall OR of 0.20 (2493 participants; 95% CI 0.05 to 0.79).

Cost

Only one study (Paventi 2001) reported total drug costs in either the BIS or CS group and the cost of BIS monitoring. The total drug cost was lower in the BIS group when compared to that in the CS group (0.699 versus 0.984 euro/min/70kg patient). (see Additional Table 2)

Table 2. Cost

Trial	Outcome	Value	BIS group	CS group	Note
Paventi 2001	Total drug cost	Euro/min	0.699	0.984	Assumption: mean drug consumption, a 70kg patient
Paventi 2001	Costs of BIS electrodes and montage of monitor	Euro/patient	14.01	-	The price in June 2000, no interest rate for the price of the device

DISCUSSION

In this review we included only 20 randomized controlled trials. Of these 20, only eight studies were considered to have high methodological quality. Anaesthesia providers participating in the trials were not blinded to the assigned group. This could introduce a 'learning contamination' bias, which is changing clinical practice in the parallel control or unmonitored group by using the information from the BIS group (Roizen 1994).

We found clinical heterogeneity regarding the anaesthetic administration, the protocol for management of insufficient anaesthesia or analgesia, and clinical end points across the studies in this review (see Additional Table 1). This could explain the statistical heterogeneity of the trial result in our review. Therefore, we decided to combine the results using the random-effects model and found that BIS-guided anaesthesia could significantly reduce anaesthetic consumption and recovery times. The higher use of anaesthetics in the standard practice group of most studies indicates that the anaesthesia providers tended to use high doses of hypnotics (in a hypnotic-based anaesthesia regimen) to manage signs of inadequate anaesthesia or analgesia which resulted in too deep anaesthesia as indicated by BIS values, in some studies (see Additional Table 3). Hence BIS-guided anaesthesia could be helpful to optimize the dose of hypnotics needed to maintain BIS values within the recommended range of 40 to 60 during maintenance of anaesthesia, or 60 to 80 at the end of surgery.

Table 3. BIS value during anaesthesia

Trial	Outcome	Value	BIS group	CS group	Note
Ahmad 2003	Bispectral index (BIS) during operation	Mean	Not applicable	Not applicable	Data not available
Basar 2003	BIS during operation	Mean	n = 30; mean = 44.9; SD (standard deviation) = 5.15	n = 30; mean = 40.5; SD =4.53	
Gan 1997	BIS index during maintenance	Mean	No	Not applicable	Data presented as graph showed BIS values at various points of anaesthesia in BIS group < in SP group
Hachero 2001	BIS index during maintenance	Median	n = 20; mean = 46.4; 95% confidence interval (CI) = 44.4 to 44.8	n = 20; mean = 42.2; 95% CI = 40.1 to 44.2	

Table 3. BIS value during anaesthesia (*Continued*)

Kreuer 2003	BIS index during maintenancee	Mean	Not applicable	Not applicable	Data presented as graph showed BIS values at various points of anaesthesia in BIS group < in SP group
Masuda 2002	BIS index during skin incision	Mean	n = 20; mean = 46; SD = 6	n = 19; mean =47; SD =10	
Masuda 2002	BIS 10 minutes before end of surgery	Mean	n = 20; mean = 59; SD = 6	n =19; mean = 52; SD = 9	
Masuda 2002	BIS at end of surgery	Mean	n = 20; mean = 69; SD = 12	n = 19; mean = 60; SD = 9	
Masuda 2002	BIS at end of anaesthesia	Mean	n = 20; mean = 92; SD = 6	n = 19; mean = 88; SD =6	
Morimoto 2002	BIS index during maintenance	Mean	Not applicable	Not applicable	Data presented as graph showed BIS values at various points of anaesthesia in BIS group < in SP group
Nelskyla 2001	BIS during surgery	Median	n = 32; median = 54; min-max = 49-61	n = 30; median = 55; min-max.=30-65	
Paventi 2001	BIS during surgery	Median	n = 45; median = 46; min-max = 36-67	n = 45; median = 42; min-max = 39-61	
Paventi 2001	BIS after skin closure	Median	n = 45; median = 62; min-max = 43-98	n = 45; median = 54; min-max = 34-99	
Recart 2003	BIS index during maintenance	Mean	n = 30; mean = 49; SD =13	n = 30; mean = 40; SD =11	
Recart 2003	BIS during emergence from anaesthesia	Mean	n = 30; mean = 88; SD =11	n = 30; mean = 88; SD =12	At the time of eye opening before removal of endotracheal tube
Song 1997	BIS index during operation	Mean	n = 15; mean = 60; SD = 4	n = 15; mean = 44; SD =11	
Song 1997	BIS during operation	Mean	n = 15; mean = 62; SD =3	n = 15; mean = 42; SD = 8	
White 2004	BIS index during maintenance	Mean	n = 20; mean = 57; SD =12	n = 20; mean = 41; SD .=10	

Table 3. BIS value during anaesthesia (*Continued*)

Wong 2002	BIS index during operation	Mean	n = 29; mean = 51; SD = 4.9	n = 31; mean = 44.3; SD = 8.8	
Wong 2002	BIS index at discontinuation of anaesthesia	Mean	n = 29; mean = 68; SD =13	n = 31; mean = 64; SD = 13	

The relatively light anaesthesia in the BIS-guided anaesthesia has raised concerns about the increased requirement of narcotic analgesics and muscle relaxants to manage clinical signs of inadequate analgesia and relaxation. However, few studies reported the significantly increased use of fentanyl (Hachero 2001) or mivacurium (Song 1997) in the BIS group, while other studies did not show any significant difference between the two groups.

The other concern when using the BIS monitoring to titrate anaesthetics is the possibility of intraoperative recall awareness during light plane anaesthesia. From this review, we did not find any reports of the incidence of intraoperative recall awareness in either the study (BIS) or control (CS) groups in trials which were conducted in surgical patients with low risk of awareness. However, the combined results from the other two studies (Myles 2004; Puri 2003), which were conducted in surgical patients with high risk of intraoperative recall awareness, provided evidence supporting the impact of BIS on reducing the incidence of intraoperative recall awareness.

The last concern regarding the use of BIS is the cost. From our systematic review, Paventi 2001 was the only randomized controlled study that directly compared the costs for the two groups. However, only the cost of drugs and BIS monitoring were compared. This did not provide sufficient evidence to support the cost-benefit of BIS monitoring. Hence, a full economic evaluation in terms of the cost-benefit of BIS monitoring in various aspects is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Anaesthesia guided by BIS, kept within the recommended range, could improve anaesthetic delivery and postoperative recovery from relatively deep anaesthesia. In addition, BIS-guided anaesthesia has significant impact on the reducing the incidence of intraoperative recall in surgical patients with high risk of awareness.

Implications for research

The information regarding the decreased anaesthetic use, recovery times and incidence of intraoperative recall awareness may be useful for further full economic evaluation in terms of the cost saving of BIS monitoring in various clinical aspects and settings in the real world.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2003

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding:no withdrawals/drop outs: 2
Participants	Country: USA N = 99 ASA: I/II gender: female age: 31.5+/-8.7,35.4+/-8.9 exclusion: not mentioned operation: gynaecologic laparoscopy duration of anaesthesia: 67+/-36; 69+/-37 min
Interventions	1) Sevoflurane inhalation guided by BIS, BIS value of 50-60 (BIS group), n = 49 2) Sevoflurane inhalation guided by clinical signs (blood pressure and heart rate) (CS group) n = 48
Outcomes	Successful fast track rate (using modified Aldrete Score, main outcome) mean concentration of sevoflurane (%, sevoflurane requirement) mean dose of sufentanil mean dose of rocuronium mean duration of phase II recovery room stay (time to discharge) incidence of pain in phase II recovery area incidence of nausea/vomiting in phase II recovery area
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Anez 2001

Methods	Quasi-randomization anaesthesiologist blinding: no assessor (observer) blinding: unclear withdrawals/dropouts: one in control group was excluded
Participants	Country: Spain N = 40 ASA: I/II

Anez 2001 (*Continued*)

	gender: ? age: 40 (average) exclusion: using psychotropic medication operation: vascular (venous) or orthopaedic outpatient surgery
Interventions	1) Propofol TCI (target controlled infusion) guided by BIS (BIS A-2000 Aspect); BIS value of 40-60, n = 20 2) Propofol administration guided by clinical signs, n = 19
Outcomes	Propofol consumption Immediate and total recovery times Presence of intraoperative alertness
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Assare 2002

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding:unclear withdrawals/drop outs: no
Participants	Country: Sweden N = 60 (20,20,20) ASA: I/II Gender: not stated Age: 45+/-12, 45+/-12, 44+/-11 (mean+/-SD) Exclusion: not state Operation: elective arthroscopy (ambulatory surgery) Duration of anaesthesia: 15+/-5, 15+/-5.5, 17+/- 4.8 (min)
Interventions	1) Sevoflurane inhalation guided by BIS (Aspect 2000, BIS Algorithm 3.4), BIS value of 60 (BIS group), n = 20 2) Sevoflurane inhalation guided by auditory evoked potential (AEP, A-Line AEP monitoring, Danmeter A/S; Odense, Denmark) (AEP group) n = 20 3) Sevoflurane inhalation guided by routine clinical signs (CS group) n = 20

Assare 2002 (*Continued*)

Outcomes	Sevoflurane consumption (g/min) Emergence times: - time to removal of laryngeal mask (min) -time to state of birth and name (min) Time to ready for discharge (min)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Basar 2003

Methods	RCT anaesthesiologist blinding:no assessor (observer) blinding: not mentioned withdrawals/drop outs: not mentioned
Participants	Country: Turkey N = 60 ASA: I/II Gender: male/female, 17/13,18/12 Age: 42.1+/-3.3, 39+/-4.5 yrs Exclusion- renal, hepatic or neurological dysfunction, use of benzodiazepines, anticonvulsants, alcohol, opioids or other psychotropic drugs Operation: open abdominal surgery Duration of anaesthesia:85+/-10.5; 90.4+/-8.7 min
Interventions	1) Sevoflurane guided by BIS (Aspect A-2000 R), BIS value of 40-60, n = 30 (BIS group) 2) Sevoflurane inhalation guided by clinical signs (blood pressure and heart rate, somatic response), n = 30 (CS group)
Outcomes	Mean sevoflurane exposure (aged adjusted minimal alveolar concentration, main outcome) Amount of sevoflurane used (ml,main outcome) Immediate recovery times (time to open eyes on verbal command, time to motor respond to verbal command) Aldrete score at 10 min
Notes	

Risk of bias

Item	Authors' judgement	Description

Basar 2003 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Gan 1997

Methods	RCT, Multicentre anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/drop outs: 28 The study had historical control group
Participants	Country: USA N = 268 ASA: I/II/III 45/65/5, 45/72/8 Gender: Male/Female 37/78,45/84 Age: 41(39-43), 40 (37-43) Exclusion: known neurologic disorders, uncontrolled hypertension,baseline systolic BP <106 HR<55, other serious medical conditions Operation: General surgical procedures> 1 hour. Duration of anaesthesia: 108 (95% CI 99 to 119); 125 (95% CI 114 to 135) min
Interventions	1) Propofol administration guided by BIS (A-100 EEG monitor, Aspect Medical Systems Inc.), BIS value of 45-60 during maintenance and 60-75 at the end of surgery (BIS group) , n = 115 2) Propofol administration guided by clinical signs (increased blood pressure of greater than 20%, increased heart rate of greater than 90 beats per minutes and other somatic responses)of inadequate anaesthesia (CS group), n =125
Outcomes	- Normalized propofol infusion rate (microgram/kg/hr) - mean propofol used (mg) -Normalized alfentanil infusion rate (microgram/kg/min) -Time to open eyes (min) -Time to respond to command (min) -Time to be extubated -Time to be eligible to discharge/readiness to home -Number of unwanted somatic and haemodynamic responses -Intraoperative global assessment score % of patients arrived fully oriented to the post anaesthesia care unit (PACU) Overall global nursing impression score
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Hachero 2001

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: probably yes withdrawals/drop outs: none
Participants	Country: Spain N = 40 ASA: I/II Gender: female Age: 18-65 years Exclusion: extreme obesity, cardiovascular and metabolic illnesses, hepatic or renal diseases and history of abuse of alcohol or drugs. Operation: gynaecologic procedures including myomectomy, hysterectomy, oophorectomy and infra umbilical laparotomy Duration of anaesthesia: 73 (64-82), 64 (56-74)
Interventions	1) Propofol administration guided by BIS (TO-2000 with electrodes BIS-Sensor, Aspect Medical Systems Inc., USA), BIS value of 40-60 during maintenance (BIS group), n = 20 2) Propofol administration guided by signs of inadequate anaesthesia (increased blood pressure of greater than 20%, increased heart rate of greater than 90 beats per minutes and other somatic or autonomic responses) (CS group), n = 20
Outcomes	-Total dose of fentanyl during maintenance (main outcome) -Propofol used during maintenance (mg)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kreuer 2003

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/drop outs: no
Participants	Country:German N = 120 ASA: I/II/III 12/25/3, 12/24/4,13/24/3 Gender: male/female 20/20,20/20,20/20 Age: 43.8+/-4.2,46.1+/-14.5,44.8+/-15.9 years. Exclusion- disabling, central nervous or cerebrovascular diseases, hypersensitivity to opioid or substance abuse, or treatment with opioids or any psychoactive medication.

Kreuer 2003 (*Continued*)

	Operation- minor orthopaedic surgery lasted at least 1 hr. Duration of anaesthesia:121.2+/-40.9; 108.2+/-44.2 min
Interventions	1) Target -controlled infusion (TCI) of propofol guided by a BIS monitor (A-2000, software version 3.2), target BIS value at 50, n = 40 2) Target -controlled infusion (TCI) of propofol guided by a Narcotrend monitor (software version 2.0 AF), target BIS value at 50, n = 40 3) Target -controlled infusion (TCI) of propofol guided by standard clinical signs, n = 40
Outcomes	-Normalized propofol infusion rate (microgram/kg/hr) -Normalized remifentanil infusion rate (microgram/kg/min) -Time to open eyes (min, primary outcome) -Time to be extubated (min) - Time to arrive in PACU (min) -Incidence of awareness (n,%) - Number of patients receiving intervention to treat intraoperative hypotension
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Luginbuhl 2003

Methods	RCT anaesthesiologist blinding: no patient blinding : yes assessor (observer) blinding: yes withdrawals/drop outs: no
Participants	Country: Switzerland N = 160 Sex: female Exclusion:central nervous system disease (i.e. history of cerebrovascular disease or epilepsy) or taking EEG-affecting drug ans ASA > 3 Operation : gynaecological surgery lasted > 15 min Desflurane subgroups -ASA: I/II/III 22/15/3, 15/22/3 -Gender: female -Age: 45.2+/-17.5,47.1+/-17.8 years. -Duration of anaesthesia: 100.5+/-58.2; 90.9+/-53.6 min Propofol subgroup (N = 80) -ASA: III/III 21/18/1, 22/16/2 -Gender: female

Luginbuhl 2003 (*Continued*)

	-Age: 46.3+/-15.4,48.7+/-15.7 years. -Duration of anaesthesia: 100.5+/-58.2; 90.9+/-53.6 min
Interventions	1) Propofol guided by BIS (Aspect A-2000-2000 monitor, BIS version 3.3 , Aspect Medical Systems, Natick, MA), BIS target value between 45 and 55 during surgery, n = 40 2) Propofol using standard clinical guide (haemodynamic and vital signs criteria), n = 40 3) Desflurane guided by BIS (Aspect A-2000 monitor, BIS version 3.3 , Aspect Medical Systems, Natick, MA), BIS target value between 45 and 55 during surgery, n = 40 4) desflurane using standard clinical guide (haemodynamic vital signs criteria), n = 40
Outcomes	Mean propofol infusion rate (mg/kg/hr) Desflurane usage (age-adjusted MAC-hours -Recovery profile - Aldrete score - Global clinical impression score - Extubation time - Duration of PACU stay
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Masuda 2002

Methods	RCT anaesthesiologist blinding: unclear assessor (observer) blinding: unclear withdrawals/drop outs: 7 (1; BIS < 80 before induction, 1; Blood loss more than 2000 ml, 3; operation time less than one hour, 1; operation time longer than three hours)
Participants	Country:Japan N = 46 ASA: I/II Gender: Female/male 15/5, 15/4 Age: 33+/-9, 37+/-14 years. Exclusion- not mentioned Operation: laparotomy (6;4), laparoscopy (7;3), surgery on extremities (5;5), arthroscopy (1;2), surface (1;1), head and neck (0;3) Duration of anaesthesia: 190+/-45, 191+/- 57

Masuda 2002 (*Continued*)

Interventions	1) Propofol infusion guided by BIS (A-1050), target BIS value at 40-60, n =20 2) Propofol guided by standard clinical signs, n =19
Outcomes	-Propofol infusion rate -Total amount of propofol used -Recovery profiles -Patients with undesirable responses
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Morimoto 2002

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: unclear withdrawals/drop outs: 14
Participants	Country: Japan N = 60 (enrolled) ASA :I/II Gender: Male/Female 21/25 Age: 18-70 Operation:not specified Duration of anaesthesia:284+/-85; 256+/172
Interventions	1) Sevoflurane guided by BIS (A 1050, version 3.4) , BIS value of 40-60 during maintenance and 60-75 at the end, n = 21 2) Sevoflurane guided by clinical signs (heart rate and blood pressure), n = 25
Outcomes	-Anaesthetic - sevoflurane consumption (ml-1) -Fentanyl required -Vecuronium required - Time to open eyes on verbal command -Time to extubate -Time to discharge from the recovery room
Notes	

Risk of bias

Item	Authors' judgement	Description

Morimoto 2002 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Myles 2004

Methods	RCT, multicentre patients blinding: yes anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/drop outs: 23 in BIS groups and 15 in SP group
Participants	Country: Australia N = 2463 ASA: I/II/III/IV 111/179/542/388/5, 127/227/520/354/10 Gender: Male/Female 752/473, 784/454 Age: 58.1 (16.5), 57.5 (16.9) Inclusion : at least one of risk factors for awareness, i.e. caesarean section, high risk cardiac surgery, acute trauma with hypovolaemia, rigid bronchoscopy, significant impairment of cardiovascular status, severe end-stage lung disease, past history of awareness, unplanned awake intubation, known or suspected heavy alcohol intake, chronic benzodiazepine or opioid use , or current protease inhibitor therapy Operation: minor/intermediate/major 104/216/905, 104/231/903 Duration of anaesthesia: 3.2 (1.5-4.4), 3.1 (1.3-4.5) hrs
Interventions	1) BIS Guided anaesthesia (A-2000, version 3.4, Aspect Medical Systems), a target BIS value of 40-60 2) Routine anaesthesia (routine care group)
Outcomes	Primary outcome: incidence of confirmed awareness Secondary outcomes: -Possible awareness -Hypnotic drug administration -Incidence of marked hypotension -Patients satisfaction -Recovery times
Notes	Relaxant general anaesthesia Induction: midazolam (62%, 62%) + propofol (63%, 63%) or thiopentone (15%, 15%) Intubation : nondepolarizing muscle relaxants (93%, 95%) Maintenance : propofol infusion (43%, 42%) nitrous oxide (35%, 37%) -opioids volatiles -hypnotic drugs (7%,6%) and combined general and regional anaesthesia (18%, 15%)
Risk of bias	

Myles 2004 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nelskyla 2001

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: no detail withdrawals/drop outs: no
Participants	Country: Finland N = 62 ASA :I/II Gender: Female Age: 32=/-6,32+/-6 Operation:gynaecologic laparoscopy (tubal ligation excluded) Duration of anaesthesia:59+/-39;55+/-50 min
Interventions	1) Sevoflurane guided by BIS (Aspect version 3.21), BIS value of 50-60, n = 32 2) Sevoflurane guided by clinical signs (blood pressure and heart rate), n = 30
Outcomes	-Incidence of nausea and vomiting (N/V) in PACU (main outcome) -Anaesthetic exposure (sevoflurane exposure, sevo-et%.h) -Number of patients required alfentanil -Time to open eyes spontaneously (min) -Time to follow command (squeezing hand) (min) -Time to be extubated (min) -Time to be eligible to discharge/home readiness
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Paventi 2001

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/drop outs: no
Participants	Country: Italy N = 90, ASA: no information Gender: no information Age: mean 42-48 years Exclusion: history of neurologic disease, medication affecting central nervous system (CNS) and alcohol and drug abuse Operation- general abdominal surgery > 30 min Duration of anaesthesia 74-102 min
Interventions	1) Sevoflurane and remifentanil administration guided by BIS (Version 3.22) of 40-60 during maintenance, n = 45 2) Anaesthetic administration without BIS information, n = 45
Outcomes	-Direct cost of anaesthesia management (total drug cost/min versus cost of BIS electrodes and monitor) (main outcome) -% sevoflurane required (median and range) -Remifentanil required, microgram/kg/hr)(median and range) -Recovery times 1. Time to breath spontaneously (min) 2. Time to be extubated (min) 3. Time to eye opening (min) 4. Time to orientation (min) -Cost 1. total drug cost/min 2. Cost of BIS electrodes (Euro/patient) -Sevoflurane requirement (median, range)
Notes	Withdrawals- not stated

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Puri 2003

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: not mentioned withdrawals/drop outs: not known
Participants	Country: India N = 30, ASA: III or greater Gender: no information Age: 38.25 +/- 14.02, 32.08+/-13.84 Inclusion: undergoing either coronary artery grafting (CAGB) or valve replacement under cardiopulmonary bypass (CP) Exclusion: neurological disorders, poor ventricular function, New York Heart Association grade IV, diabetes mellitus, and impaired renal or hepatic function Operation: coronary artery grafting (CAGB) or valve replacement under cardiopulmonary bypass (CP) Duration of surgery 295+/-45, 285+/-40 minutes
Interventions	1) Isoflurane administration guided by BIS (Aspect A-1000, version 3.1) of 45 to 55 2) Isoflurane administration guided by clinical signs
Outcomes	-Number of haemodynamics disturbances: hypertension, tachycardia, hypotension, bradycardia -Recovery end point -Time to tracheal extubation -Awareness
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Recart 2003

Methods	Randomizations: yes anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/dropouts: no
Participants	Country: USA N = 90 ASA: NA Gender: Male/Female 21/9,20/10,24/6 Age: 47+/-17,46+/-15,42+/-14 Exclusion: history of CNS disease, chronic use of psychoactive medication, and clinical significant cardiovascular, renal, hepatic or endocrinology disorders

Recart 2003 (*Continued*)

	Operation: laparoscopic general surgery procedures (choleycycstectomy, gastric bypass/banding, hernia repair) Duration of anaesthesia: 125+/- 52; 127+/-38 min
Interventions	1) Desflurane guided by BIS (BIS TM sensor XP, Aspect Medical Systems, Newton, MA) for maintaining BIS values of 45-55 2) Desflurane guided by clinical signs 3) Desflurane guided by auditory evoked potential index (AAI)
Outcomes	- End tidal concentrations of desflurane (%) (main outcome) -Total fentanyl used -Total rocuronium used (mg) - Requirement of labetalol (n,%) -Time to open eyes -Time to obey simple verbal commands -Time to orientation -Time to be extubated -Time to achieve White fast-track score > or = 12 -Time to achieve Aldrete discharge score of 10 -Length of stay in the post anaesthesia care unit (PACU) -Patients with recall of intraoperative awareness (n,%)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Song 1997

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: no withdrawals/drop outs: no
Participants	Country: USA N = 60 (30 sevoflurane, 30 desflurane) Sex : female Exclusion- Neurologic disease, CVS or metabolic diseases, impaired renal or hepatic function, BW > 100% above the ideal or history of alcohol or drug abuse Operation: laparoscopic tubal ligation Desflurane subgroup (treatment , control) -ASA: I/II , 10/5, 11/4 -Age: 28+/-4, 27+/-6 -Duration of anaesthesia:76+/-20;78+/-22 min

Song 1997 (*Continued*)

	Sevoflurane-sub group; treatment, control -ASA: I/II ; 11/4, 10/5 -Age: 26+/-6, 26+/-7 -Duration of anaesthesia:74+/-21; 75+/- 21 min.
Interventions	1) Desflurane guided by BIS (Rev 3.12U; Model A -1050, Aspect Medical Systems, Natick, MA)) at value of 60 2) Desflurane using standard clinical guide 3) Sevoflurane guided by BIS BIS (Rev3.12U ; Model A -1050, Aspect Medical Systems,Natick,MA)at value of 60 4) Sevoflurane using standard clinical guide
Outcomes	-End tidal concentration (%) -Exposure to desflurane (MAC. hrs) -Consumption of desflurane (ml) -Consumption of mivacurium (mg) -Consumption of fentanyl (microgram) -Time to verbal response (min) -Time to extubation (min) -Time to orientation (min) -Time to PACU stay (min) -Time to oral intake (min) -Time to home readiness (min) -Patients with recall awareness - Patients with increased airway pressure -Patient with coughing and bucking
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Struys 2001

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: unclear withdrawals/drop outs: no
Participants	Country: Belgium N = 20 Sex : female Exclusion-neurologic disorders, psychoactive medication including alcohol, body weight above 130% or below 70% of the ideal body weight Operation: gynaecologic laparotomy

Struys 2001 (*Continued*)

	-ASA: I/II -Age: 42+/-8, 46+/-4 -Duration of anaesthesia:6798+/-2085; 6896+/-2018 second
Interventions	1) Closed-loop controlled administration of propofol guided by BIS (A-2000; Aspect Medical Systems Inc,Version 3.4) at value to 50 2) Manual administration of propofol guided by classical signs of (in) adequate anaesthesia
Outcomes	-Time to spontaneous breathing -Time to eye opening -Time to extubation -Time to orientation -Propofol use (mg/kg/hr)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tufano 2000

Methods	RCT anaesthesiologist blinding: unclear assessors (observer) blinding: yes withdrawals/drop outs: not mentioned
Participants	Country: Italy N = 160 (80 propofol, 80 sevoflurane) ASA? Gender? Age 18-70 Operation: abdominal surgery
Interventions	1) Propofol guided by BIS 2) Propofol guided by clinical signs 3) Sevoflurane guided by BIS 4) Sevoflurane guided by clinical signs
Outcomes	-Propofol or sevoflurane consumption -Fentanyl consumption -Time to spontaneous breathing -Time to extubation -Time to follow simple commands

Tufano 2000 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

White 2004

Methods	RCT anaesthesiologist blinding: no assessor (observer) blinding: yes withdrawals/drop outs: no
Participants	Country:USA N = 60 ASA I/II/II 9/10/1 9/11/0,7/12/1 Gender: female Exclusion: known neurologic or psychiatric disorders, currently using anticonvulsants or other centrally actives medications, clinically significant cardiovascular, respiratory, hepatic, renal or metabolic diseases, long term drug or alcohol abuse; or a body weight greater than 50% above the ideal body weight Operation:Gynaecologic laparoscopic surgery Duration of anaesthesia:58+/-22; 66+/-16 min
Interventions	1) Desflurane guided by BIS, BIS value of 50-60 2)Desflurane guided by standard clinical signs (maintaining haemodynamic stability, avoiding movement and achieving a rapid recovery) 3) BIS guided by auditory evoked potential index (AAI)
Outcomes	-End tidal concentration -Desflurane consumption (ml) -Time to open eyes (main outcome) -Time to follow simple commands (e.g. squeeze the investigator's hand) -Time to orientation -White fast-track score on arrival in PACU -Modified Aldrete score on arrival in PACU -Time to fit for discharge (sitting up, standing, ambulating and tolerating oral fluids) -Actual discharge time- -Quality recovery score before discharge -Intraoperative recall
Notes	

Risk of bias

Item	Authors' judgement	Description

White 2004 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Wong 2002

Methods	RCT anaesthesiologist blinding: no patient blinding: yes assessor (observer) blinding: yes withdrawals/drop outs: 8
Participants	Country: Canada N = 68 ASA:I/II/II 2/24/3 , 3/27/1 Gender: Male/Female 10/10,21/10 Age: 71+/15,70+/-6 Exclusion- significant cardiopulmonary diseases or other end-organ disease, depression or psychiatric disorders, dementia previous CVA, head trauma, inadequate command of English and drugs and all alcohol abuse, preoperative baseline of Mini Mental state exam (MMSE) <24 Operation- elective orthopedic surgery or hip replacement. Duration of anaesthesia:120+/-17; 121+/-17 min
Interventions	1) Administration of isoflurane and fentanyl to Maintain BIS index of 50-60 (model A1050, Aspect Medical System), n = 29 2) Administration of isoflurane and fentanyl adjusted to clinical practice and to provide rapid recovery, n = 31
Outcomes	-Time to orientation to person, place and time (main outcome) -End tidal concentration (%) -Consumption of isoflurane (ml) - Time to awakening (eye opening to verbal commands) -Time to extubation -Time to readiness for transfer to postanaesthetic care unit -Time to readiness for discharge from PACU (Aldrete score >9) -symptoms of postoperative cognitive dysfunction -recall awareness of intraoperative events
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

RCT = randomized controlled trial
BIS = Bispectral index

TCI = target controlled infusion

Characteristics of excluded studies *[ordered by study ID]*

Burrow 2001	The study was not a RCT.
Guignard 2001	The study was not a RCT (historical control).
Johansen 2000	The study was not a RCT. It was an open, observational trial with retrospective analysis.
Lehmann 2003	This study was a RCT but compared 2 levels of BIS-guided anaesthesia. The control group was not taken into consideration in this study.
Pavlin 2001	The study was a RCT but the randomization was different from the other studies. It allocated health care providers to use or not use BIS for guiding doses of anaesthetics. Therefore, the study design did not fulfil the inclusion criteria of the study selection in terms of randomization process.
Sebel 1997	It was a multicentre RCT to evaluate the real-time utility of BIS in predicting movement response incision. Hence, it did not fulfil the objective of this review.
Song 1998	This study was a RCT but did not use BIS guiding doses of anaesthetics but used it as a tool to measure the effect of two anaesthetics.
Yli-Hankala 1999	This study was an RCT but was excluded as it randomly allocated participant into two groups based on the anaesthetic use (propofol versus sevoflurane). The comparison group was a historical control group.

RCT = randomized controlled trial
BIS = bispectral index

DATA AND ANALYSES

Comparison 1. Anaesthetic requirement or consumption (bispectral index versus clinical signs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Normalized propofol infusion rate (mg/kg/hr)	7	578	Mean Difference (IV, Random, 95% CI)	-1.30 [-1.97, -0.62]
2 Volatile anaesthetic requirement, minimal alveolar concentration equivalents (MAC equivalents)	10	689	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.27, -0.07]
2.1 desflurane	4	210	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.30, -0.02]
2.2 isoflurane	1	60	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.29, 0.05]
2.3 sevoflurane	6	419	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]

Comparison 2. Recovery profiles (bispectral index versus clinical signs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to eyes opening (minutes)	13	996	Mean Difference (IV, Random, 95% CI)	-2.43 [-3.60, -1.27]
1.1 propofol	6	498	Mean Difference (IV, Random, 95% CI)	-4.24 [-5.20, -3.28]
1.2 desflurane	2	100	Mean Difference (IV, Random, 95% CI)	-2.0 [-3.84, -0.16]
1.3 isoflurane	1	60	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.32, 0.52]
1.4 sevoflurane	5	338	Mean Difference (IV, Random, 95% CI)	-1.15 [-2.61, 0.32]
2 Time to respond to verbal command (minutes)	10	717	Mean Difference (IV, Random, 95% CI)	-2.28 [-3.47, -1.09]
2.1 propofol	3	359	Mean Difference (IV, Random, 95% CI)	-3.82 [-5.36, -2.29]
2.2 desflurane	3	130	Mean Difference (IV, Random, 95% CI)	-3.38 [-4.68, -2.07]
2.3 isoflurane	1	60	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.32, 0.52]
2.4 sevoflurane	3	168	Mean Difference (IV, Random, 95% CI)	-1.14 [-3.26, 0.97]
3 Time to extubation (minutes)	12	1057	Mean Difference (IV, Random, 95% CI)	-3.05 [-3.98, -2.11]
3.1 propofol	6	539	Mean Difference (IV, Random, 95% CI)	-4.53 [-5.72, -3.33]
3.2 desflurane	4	210	Mean Difference (IV, Random, 95% CI)	-2.82 [-4.06, -1.59]
3.3 isoflurane	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.4 sevoflurane	5	308	Mean Difference (IV, Random, 95% CI)	-2.15 [-3.71, -0.59]
4 Time to orientation (minutes)	6	316	Mean Difference (IV, Fixed, 95% CI)	-2.46 [-3.21, -1.71]
4.1 propofol	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.19 [-19.95, 15.57]
4.2 desflurane	2	70	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.23, -0.97]
4.3 isoflurane	1	44	Mean Difference (IV, Fixed, 95% CI)	-3.6 [-5.92, -1.28]
4.4 sevoflurane	3	182	Mean Difference (IV, Fixed, 95% CI)	-2.24 [-3.15, -1.33]
5 PACU stay (minutes)	8	584	Mean Difference (IV, Random, 95% CI)	-6.83 [-12.08, -1.58]
5.1 propofol	3	318	Mean Difference (IV, Random, 95% CI)	-5.84 [-10.07, -1.62]
5.2 desflurane	3	130	Mean Difference (IV, Random, 95% CI)	-31.01 [-70.34, 8.32]

5.3 isoflurane	1	60	Mean Difference (IV, Random, 95% CI)	-14.00 [-34.12, 6.12]
5.4 sevoflurane	2	76	Mean Difference (IV, Random, 95% CI)	-2.99 [-11.75, 5.78]
6 Time to home readiness (minutes)	6	329	Mean Difference (IV, Random, 95% CI)	-7.01 [-30.11, 16.09]
6.1 propofol	1	39	Mean Difference (IV, Random, 95% CI)	-5.36 [-33.01, 22.29]
6.2 isoflurane	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
6.3 desflurane	2	70	Mean Difference (IV, Random, 95% CI)	-30.93 [-107.35, 45.48]
6.4 sevoflurane	4	220	Mean Difference (IV, Random, 95% CI)	8.93 [-4.49, 22.35]

Comparison 3. Requirement of nacrotics (bispectral index versus clinical signs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total dose of fentanyl (microgramme)	6	276	Mean Difference (IV, Random, 95% CI)	18.02 [-25.16, 61.20]

Comparison 4. Requirement of neuromuscular blocking agents (bispectral index versus clinical signs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 mivacurium (mg)	1	60	Mean Difference (IV, Fixed, 95% CI)	5.32 [2.95, 7.69]
1.1 desflurane	1	30	Mean Difference (IV, Fixed, 95% CI)	5.70 [2.77, 8.63]
1.2 sevoflurane	1	30	Mean Difference (IV, Fixed, 95% CI)	4.6 [0.56, 8.64]

Comparison 5. Incidence of awareness in surgical patients with risk of awareness (bispectral index versus clinical signs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of awareness (%)	2	2493	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.05, 0.79]

Analysis 1.1. Comparison 1 Anaesthetic requirement or consumption (bispectral index versus clinical signs), Outcome 1 Normalized propofol infusion rate (mg/kg/hr).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

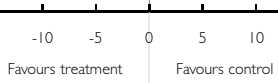
Comparison: 1 Anaesthetic requirement or consumption (bispectral index versus clinical signs)

Outcome: 1 Normalized propofol infusion rate (mg/kg/hr)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Anez 2001	20	8.04 (2.52)	19	11.94 (2.28)		10.0 %	-3.90 [-5.41, -2.39]
Gan 1997	115	6.96 (1.98)	125	8.04 (1.74)		18.1 %	-1.08 [-1.55, -0.61]
Kreuer 2003	40	4.8 (1)	40	6.8 (1.2)		18.0 %	-2.00 [-2.48, -1.52]
Luginbuhl 2003	40	6.03 (1.4)	40	6.64 (0.9)		17.8 %	-0.61 [-1.13, -0.09]
Masuda 2002	20	4.3 (1.1)	19	4.9 (0.8)		17.2 %	-0.60 [-1.20, 0.00]
Struys 2001	10	6.39 (1.13)	10	6.48 (1.59)		12.1 %	-0.09 [-1.30, 1.12]
Tufano 2000	40	5.88 (4.8)	40	7.8 (4.8)		6.8 %	-1.92 [-4.02, 0.18]
Total (95% CI)	**285**		**293**			**100.0 %**	**-1.30 [-1.97, -0.62]**

Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 35.57$, df = 6 (P<0.00001); $I^2 = 83\%$

Test for overall effect: Z = 3.78 (P = 0.00016)



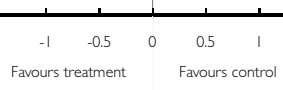
Analysis 1.2. Comparison 1 Anaesthetic requirement or consumption (bispectral index versus clinical signs), Outcome 2 Volatile anaesthetic requirement, minimal alveolar concentration equivalents (MAC equivalents).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 1 Anaesthetic requirement or consumption (bispectral index versus clinical signs)

Outcome: 2 Volatile anaesthetic requirement, minimal alveolar concentration equivalents (MAC equivalents)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 desflurane							
Luginbuhl 2003	40	0.47 (0.1)	40	0.51 (0.08)		12.8 %	-0.04 [-0.08, 0.00]
Recart 2003	30	0.65 (0.1)	30	0.78 (0.12)		12.5 %	-0.13 [-0.19, -0.07]
Song 1997	15	0.38 (0.08)	15	0.7 (0.07)		12.6 %	-0.32 [-0.37, -0.27]
White 2004	20	0.45 (0.15)	20	0.6 (0.25)		10.8 %	-0.15 [-0.28, -0.02]
Subtotal (95% CI)	**105**		**105**			**48.7 %**	**-0.16 [-0.30, -0.02]**
Heterogeneity: Tau² = 0.02; Chi² = 67.50, df = 3 (P<0.00001); I² =96%							
Test for overall effect: Z = 2.26 (P = 0.024)							
2 isoflurane							
Wong 2002	29	0.34 (0.43)	31	0.46 (0.17)		9.6 %	-0.12 [-0.29, 0.05]
Subtotal (95% CI)	**29**		**31**			**9.6 %**	**-0.12 [-0.29, 0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.40 (P = 0.16)							
3 sevoflurane							
Ahmad 2003	49	1.19 (0.14)	48	1.21 (0.48)		10.4 %	-0.02 [-0.16, 0.12]
Basar 2003	30	0.81 (0.11)	30	0.84 (0.14)		12.4 %	-0.03 [-0.09, 0.03]
Nelskyla 2001	32	0.28 (1.11)	30	0.27 (1.61)		1.8 %	0.01 [-0.68, 0.70]
Paventi 2001	45	0.46 (2.42)	45	1.12 (2.42)		0.9 %	-0.66 [-1.66, 0.34]
Song 1997	15	0.5 (0.17)	15	1 (0.17)		11.0 %	-0.50 [-0.62, -0.38]
Tufano 2000	40	0.47 (0.78)	40	0.78 (0.78)		5.2 %	-0.31 [-0.65, 0.03]
Subtotal (95% CI)	**211**		**208**			**41.7 %**	**-0.21 [-0.45, 0.03]**
Heterogeneity: Tau² = 0.06; Chi² = 49.50, df = 5 (P<0.00001); I² =90%							
Test for overall effect: Z = 1.72 (P = 0.085)							
Total (95% CI)	**345**		**344**			**100.0 %**	**-0.17 [-0.27, -0.07]**
Heterogeneity: Tau² = 0.02; Chi² = 117.33, df = 10 (P<0.00001); I² =91%							
Test for overall effect: Z = 3.35 (P = 0.00081)							



Analysis 2.1. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 1 Time to eyes opening (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 1 Time to eyes opening (minutes)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 propofol							
Anez 2001	20	4.63 (2.31)	19	8.7 (2.97)		9.9 %	-4.07 [-5.75, -2.39]
Gan 1997	115	6.25 (5.19)	125	9.52 (7.89)		9.9 %	-3.27 [-4.95, -1.59]
Kreuer 2003	40	3.5 (2.9)	40	9.3 (5.2)		9.5 %	-5.80 [-7.65, -3.95]
Masuda 2002	20	8.1 (6.9)	19	10.9 (7.5)		4.3 %	-2.80 [-7.33, 1.73]
Struys 2001	10	5.6 (3.1)	10	9.45 (28.21)		0.4 %	-3.85 [-21.44, 13.74]
Tufano 2000	40	3.4 (11.67)	40	8.13 (11.67)		3.7 %	-4.73 [-9.84, 0.38]
Subtotal (95% CI)	**245**		**253**			**37.7 %**	**-4.24 [-5.20, -3.28]**
Heterogeneity: Tau² = 0.0; Chi² = 4.50, df = 5 (P = 0.48); I² =0.0%							
Test for overall effect: Z = 8.70 (P < 0.00001)							
2 desflurane							
Recart 2003	30	6 (5)	30	8 (8)		6.1 %	-2.00 [-5.38, 1.38]
White 2004	20	7 (3)	20	9 (4)		8.6 %	-2.00 [-4.19, 0.19]
Subtotal (95% CI)	**50**		**50**			**14.7 %**	**-2.00 [-3.84, -0.16]**
Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%							
Test for overall effect: Z = 2.13 (P = 0.033)							
3 isoflurane							
Wong 2002	29	4 (2.1)	31	4.9 (3.4)		10.5 %	-0.90 [-2.32, 0.52]
Subtotal (95% CI)	**29**		**31**			**10.5 %**	**-0.90 [-2.32, 0.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.24 (P = 0.21)							
4 sevoflurane							
Basar 2003	30	8.25 (1.8)	30	8.59 (1.02)		11.8 %	-0.34 [-1.08, 0.40]
Morimoto 2002	21	3 (1)	25	6 (3)		10.9 %	-3.00 [-4.25, -1.75]
Nelskyla 2001	32	5 (2)	30	5 (2)		11.4 %	0.0 [-1.00, 1.00]
Paventi 2001	45	3 (21.01)	45	6 (21.01)		1.6 %	-3.00 [-11.68, 5.68]
Tufano 2000	40	3.48 (21.39)	40	6.68 (21.39)		1.4 %	-3.20 [-12.57, 6.17]
Subtotal (95% CI)	**168**		**170**			**37.1 %**	**-1.15 [-2.61, 0.32]**
Heterogeneity: Tau² = 1.50; Chi² = 16.30, df = 4 (P = 0.003); I² =75%							

(*Continued . . .*)

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Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.53 (P = 0.12)							
Total (95% CI)	**492**		**504**		◆	**100.0 %**	**-2.43 [-3.60, -1.27]**
Heterogeneity: Tau^2 = 2.85; Chi^2 = 60.93, df = 13 (P<0.00001); I^2 =79%							
Test for overall effect: Z = 4.09 (P = 0.000043)							

-10 -5 0 5 10

Favours treatment Favours control

Analysis 2.2. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 2 Time to respond to verbal command (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 2 Time to respond to verbal command (minutes)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 propofol							
Gan 1997	115	6.65 (5.47)	125	10.47 (7.59)	■	11.5 %	-3.82 [-5.48, -2.16]
Masuda 2002	20	8.7 (7)	19	11.4 (7.5)	■	4.7 %	-2.70 [-7.26, 1.86]
Tufano 2000	40	6.4 (17.52)	40	13.5 (17.52)	■	2.1 %	-7.10 [-14.78, 0.58]
Subtotal (95% CI)	**175**		**184**		◆	**18.3 %**	**-3.82 [-5.36, -2.29]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.93, df = 2 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 4.89 (P < 0.00001)							
2 desflurane							
Recart 2003	30	7 (4)	30	12 (9)	■	6.5 %	-5.00 [-8.52, -1.48]
Song 1997	15	2.8 (1.2)	15	6 (3.4)	■	11.0 %	-3.20 [-5.02, -1.38]
White 2004	20	7 (3)	20	10 (4)	■	9.9 %	-3.00 [-5.19, -0.81]
Subtotal (95% CI)	**65**		**65**		◆	**27.4 %**	**-3.38 [-4.68, -2.07]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.96, df = 2 (P = 0.62); I^2 =0.0%							
Test for overall effect: Z = 5.08 (P < 0.00001)							
3 isoflurane							
Wong 2002	29	4 (2.1)	31	4.9 (3.4)	■	12.3 %	-0.90 [-2.32, 0.52]
Subtotal (95% CI)	**29**		**31**		◆	**12.3 %**	**-0.90 [-2.32, 0.52]**
Heterogeneity: not applicable							

-10 -5 0 5 10

Favours treatment Favours control

(*Continued* . . .)

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Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.24 (P = 0.21)							
4 sevoflurane							
Basar 2003	30	8.25 (1.8)	30	8.59 (1.02)		14.1 %	-0.34 [-1.08, 0.40]
Morimoto 2002	21	3 (1)	25	6 (0.03)		14.6 %	-3.00 [-3.43, -2.57]
Nelskyla 2001	32	5 (2)	30	5 (2)		13.5 %	0.0 [-1.00, 1.00]
Subtotal (95% CI)	**83**		**85**			**42.1 %**	**-1.14 [-3.26, 0.97]**
Heterogeneity: Tau² = 3.35; Chi² = 55.70, df = 2 (P<0.00001); I² =96%							
Test for overall effect: Z = 1.06 (P = 0.29)							
Total (95% CI)	**352**		**365**			**100.0 %**	**-2.28 [-3.47, -1.09]**
Heterogeneity: Tau² = 2.49; Chi² = 68.87, df = 9 (P<0.00001); I² =87%							
Test for overall effect: Z = 3.75 (P = 0.00017)							

Analysis 2.3. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 3 Time to extubation (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 3 Time to extubation (minutes)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 propofol							
Gan 1997	115	7.27 (5.52)	125	11.22 (14.33)		6.8 %	-3.95 [-6.66, -1.24]
Kreuer 2003	40	4.1 (2.9)	40	9.7 (5.3)		9.6 %	-5.60 [-7.47, -3.73]
Luginbuhl 2003	40	6.8 (4.6)	40	10.5 (5.9)		8.0 %	-3.70 [-6.02, -1.38]
Masuda 2002	20	10.8 (6.9)	19	13.8 (7.8)		3.2 %	-3.00 [-7.63, 1.63]
Struys 2001	10	6.91 (2.96)	10	9.67 (28.35)		0.3 %	-2.76 [-20.43, 14.91]
Tufano 2000	40	2.78 (11.4)	40	7.4 (11.4)		2.9 %	-4.62 [-9.62, 0.38]
Subtotal (95% CI)	**265**		**274**			**30.7 %**	**-4.53 [-5.72, -3.33]**
Heterogeneity: Tau² = 0.0; Chi² = 2.38, df = 5 (P = 0.79); I² =0.0%							
Test for overall effect: Z = 7.41 (P < 0.00001)							

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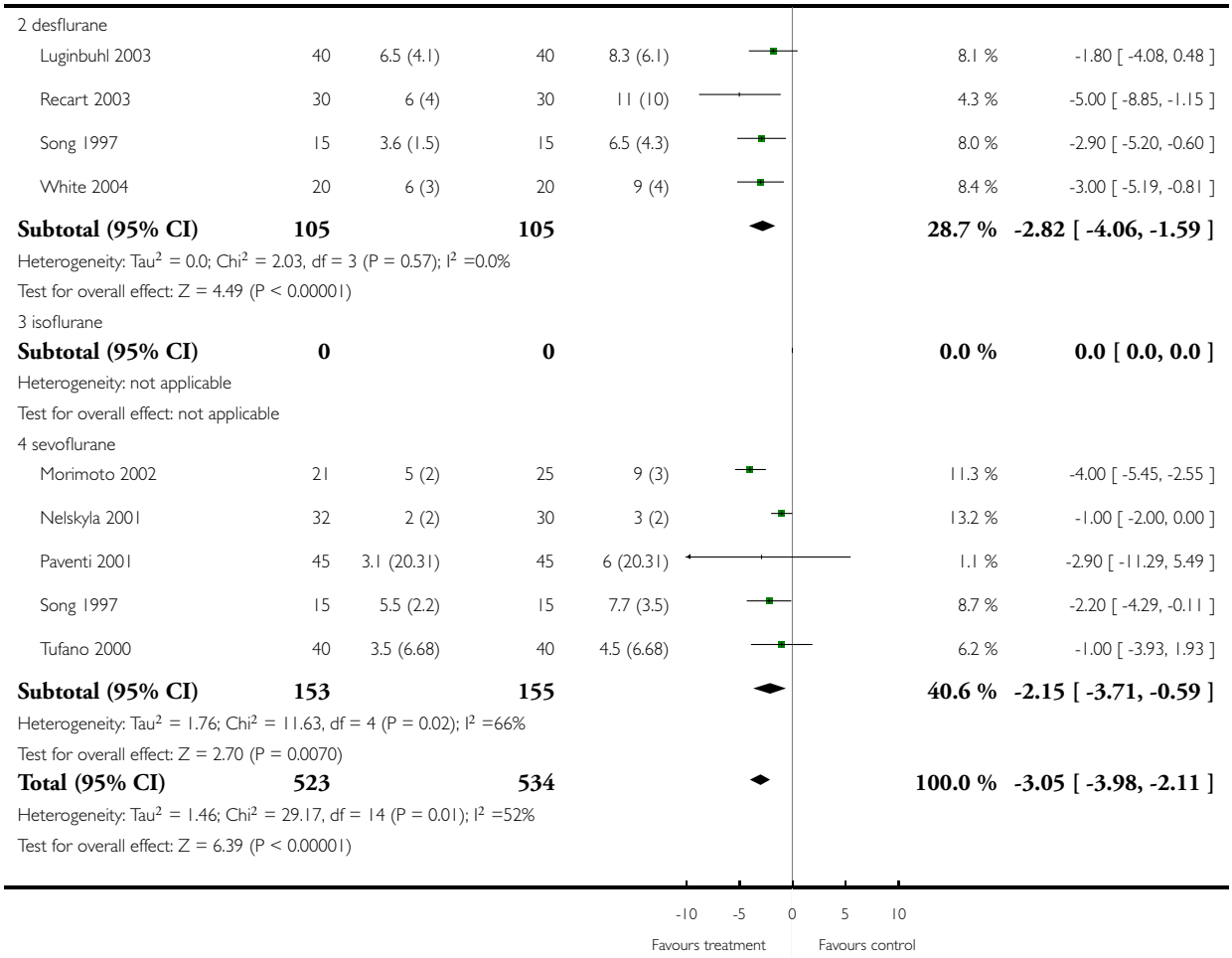
Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
2 desflurane							
Luginbuhl 2003	40	6.5 (4.1)	40	8.3 (6.1)		8.1 %	-1.80 [-4.08, 0.48]
Recart 2003	30	6 (4)	30	11 (10)		4.3 %	-5.00 [-8.85, -1.15]
Song 1997	15	3.6 (1.5)	15	6.5 (4.3)		8.0 %	-2.90 [-5.20, -0.60]
White 2004	20	6 (3)	20	9 (4)		8.4 %	-3.00 [-5.19, -0.81]
Subtotal (95% CI)	**105**		**105**			**28.7 %**	**-2.82 [-4.06, -1.59]**
Heterogeneity: Tau² = 0.0; Chi² = 2.03, df = 3 (P = 0.57); I² =0.0%							
Test for overall effect: Z = 4.49 (P < 0.00001)							
3 isoflurane							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
4 sevoflurane							
Morimoto 2002	21	5 (2)	25	9 (3)		11.3 %	-4.00 [-5.45, -2.55]
Nelskyla 2001	32	2 (2)	30	3 (2)		13.2 %	-1.00 [-2.00, 0.00]
Paventi 2001	45	3.1 (20.31)	45	6 (20.31)		1.1 %	-2.90 [-11.29, 5.49]
Song 1997	15	5.5 (2.2)	15	7.7 (3.5)		8.7 %	-2.20 [-4.29, -0.11]
Tufano 2000	40	3.5 (6.68)	40	4.5 (6.68)		6.2 %	-1.00 [-3.93, 1.93]
Subtotal (95% CI)	**153**		**155**			**40.6 %**	**-2.15 [-3.71, -0.59]**
Heterogeneity: Tau² = 1.76; Chi² = 11.63, df = 4 (P = 0.02); I² =66%							
Test for overall effect: Z = 2.70 (P = 0.0070)							
Total (95% CI)	**523**		**534**			**100.0 %**	**-3.05 [-3.98, -2.11]**
Heterogeneity: Tau² = 1.46; Chi² = 29.17, df = 14 (P = 0.01); I² =52%							
Test for overall effect: Z = 6.39 (P < 0.00001)							

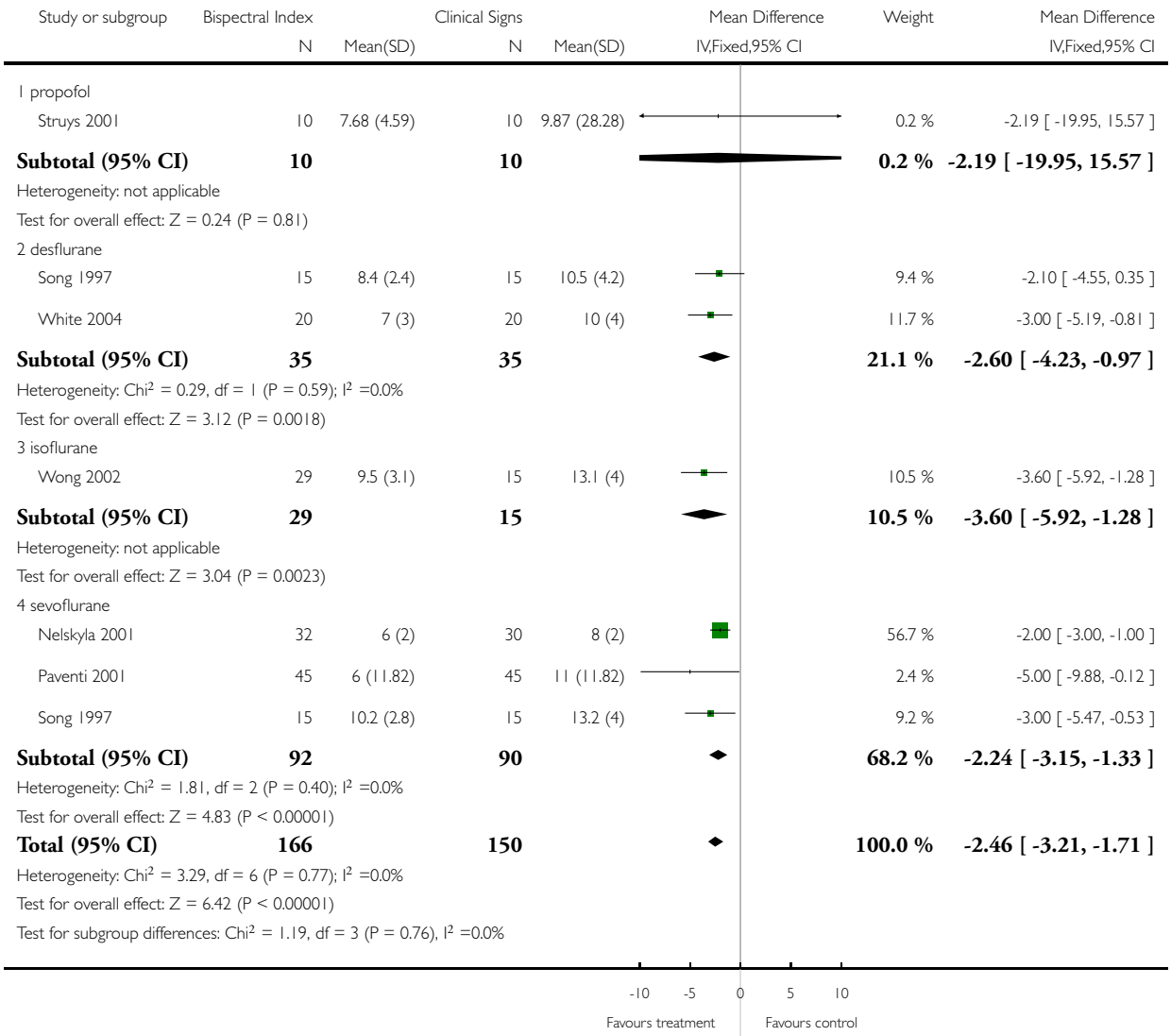


Analysis 2.4. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 4 Time to orientation (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 4 Time to orientation (minutes)



Analysis 2.5. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 5 PACU stay (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 5 PACU stay (minutes)

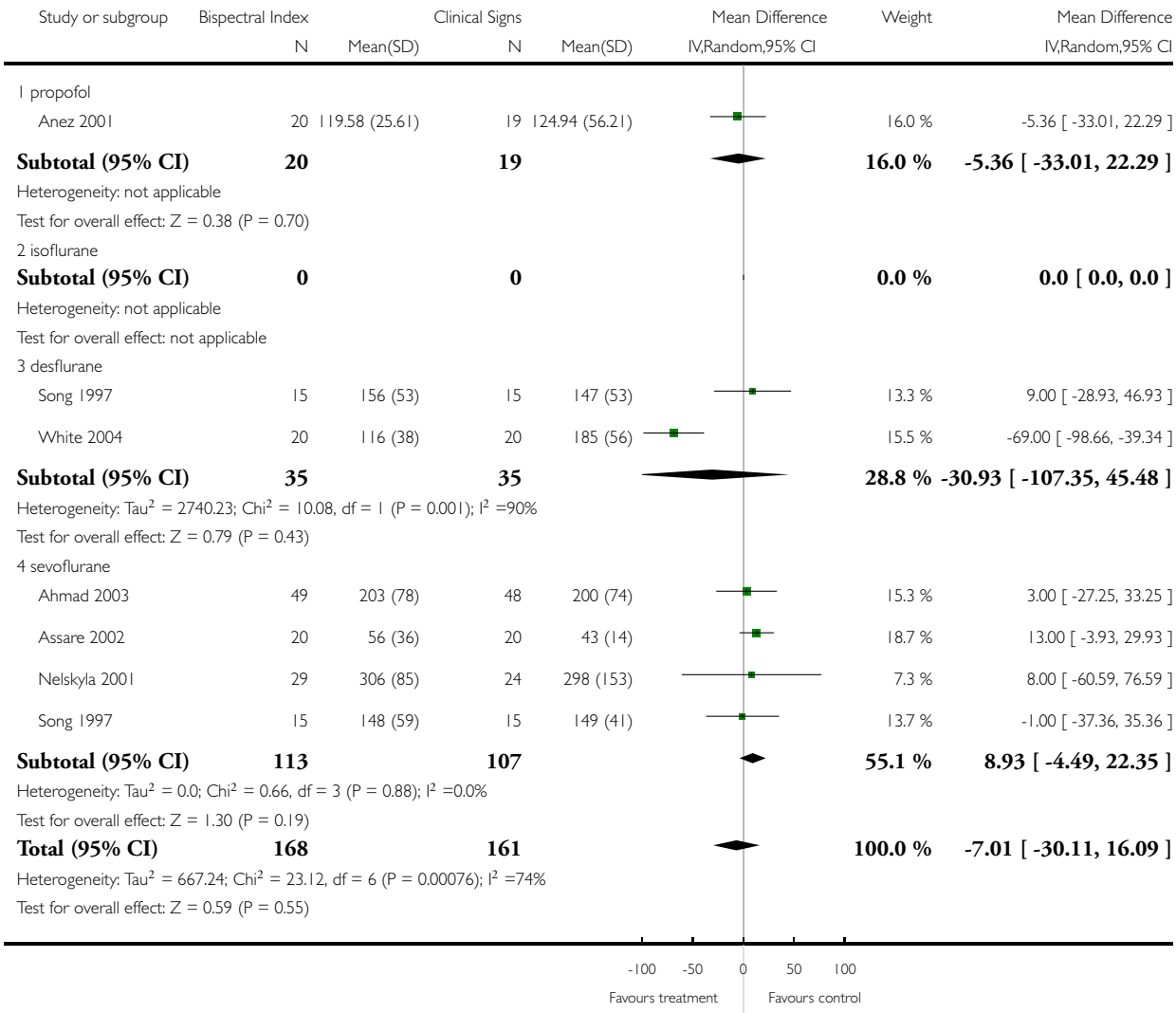
Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 propofol							
Anez 2001	20	50.05 (22.7)	19	49.26 (14.32)		9.8 %	0.79 [-11.06, 12.64]
Gan 1997	115	31.7 (20.13)	125	37.78 (23.5)		16.2 %	-6.08 [-11.60, -0.56]
Masuda 2002	20	22.3 (12.6)	19	30.6 (12.5)		13.7 %	-8.30 [-16.18, -0.42]
Subtotal (95% CI)	**155**		**163**			**39.7 %**	**-5.84 [-10.07, -1.62]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.58$, df = 2 (P = 0.45); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.71 (P = 0.0067)							
2 desflurane							
Recart 2003	30	80 (47)	30	108 (58)		3.2 %	-28.00 [-54.71, -1.29]
Song 1997	15	35 (8)	15	37 (9)		15.6 %	-2.00 [-8.09, 4.09]
White 2004	20	116 (38)	20	185 (56)		2.7 %	-69.00 [-98.66, -39.34]
Subtotal (95% CI)	**65**		**65**			**21.5 %**	**-31.01 [-70.34, 8.32]**
Heterogeneity: $Tau^2 = 1074.21$; $Chi^2 = 21.59$, df = 2 (P = 0.00002); $I^2 = 91\%$							
Test for overall effect: Z = 1.55 (P = 0.12)							
3 isoflurane							
Wong 2002	29	111 (30)	31	125 (48)		5.1 %	-14.00 [-34.12, 6.12]
Subtotal (95% CI)	**29**		**31**			**5.1 %**	**-14.00 [-34.12, 6.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.36 (P = 0.17)							
4 sevoflurane							
Morimoto 2002	21	16 (4)	25	23 (6)		18.6 %	-7.00 [-9.91, -4.09]
Song 1997	15	37 (10)	15	35 (8)		15.2 %	2.00 [-4.48, 8.48]
Subtotal (95% CI)	**36**		**40**			**33.8 %**	**-2.99 [-11.75, 5.78]**
Heterogeneity: $Tau^2 = 33.93$; $Chi^2 = 6.17$, df = 1 (P = 0.01); $I^2 = 84\%$							
Test for overall effect: Z = 0.67 (P = 0.50)							
Total (95% CI)	**285**		**299**			**100.0 %**	**-6.83 [-12.08, -1.58]**
Heterogeneity: $Tau^2 = 36.39$; $Chi^2 = 30.02$, df = 8 (P = 0.00021); $I^2 = 73\%$							
Test for overall effect: Z = 2.55 (P = 0.011)							

Analysis 2.6. Comparison 2 Recovery profiles (bispectral index versus clinical signs), Outcome 6 Time to home readiness (minutes).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 2 Recovery profiles (bispectral index versus clinical signs)

Outcome: 6 Time to home readiness (minutes)



Analysis 3.1. Comparison 3 Requirement of nacrotics (bispectral index versus clinical signs), Outcome 1 Total dose of fentanyl (microgramme).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 3 Requirement of nacrotics (bispectral index versus clinical signs)

Outcome: 1 Total dose of fentanyl (microgramme)

Study or subgroup	Bispectral Index N	Mean(SD)	Clinical Signs N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hachero 2001	20	415 (95.55)	20	253 (95.55)		15.5 %	162.00 [102.78, 221.22]
Morimoto 2002	21	132 (80)	25	129 (64)		18.1 %	3.00 [-39.43, 45.43]
Recart 2003	30	316 (148)	30	373 (201)		11.3 %	-57.00 [-146.32, 32.32]
Song 1997	15	134 (81)	15	146 (78)		15.9 %	-12.00 [-68.91, 44.91]
White 2004	20	86 (33)	20	80 (30)		20.9 %	6.00 [-13.55, 25.55]
Wong 2002	29	307 (64)	31	310 (95)		18.3 %	-3.00 [-43.75, 37.75]
Total (95% CI)	**135**		**141**			**100.0 %**	**18.02 [-25.16, 61.20]**

Heterogeneity: $Tau^2 = 2217.95$; $Chi^2 = 28.67$, df = 5 (P = 0.00003); $I^2 = 83\%$

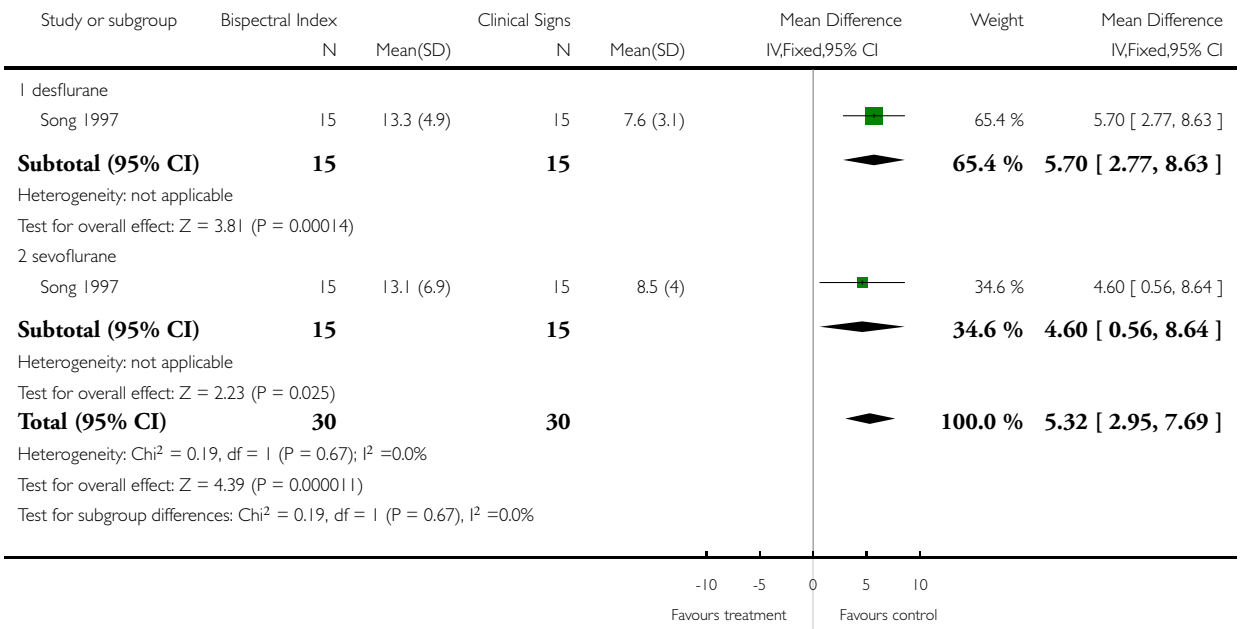
Test for overall effect: Z = 0.82 (P = 0.41)

Analysis 4.1. Comparison 4 Requirement of neuromuscular blocking agents (bispectral index versus clinical signs), Outcome 1 mivacurium (mg).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 4 Requirement of neuromuscular blocking agents (bispectral index versus clinical signs)

Outcome: 1 mivacurium (mg)



Analysis 5.1. Comparison 5 Incidence of awareness in surgical patients with risk of awareness (bispectral index versus clinical signs), Outcome 1 Incidence of awareness (%).

Review: Bispectral index for improving anaesthetic delivery and postoperative recovery

Comparison: 5 Incidence of awareness in surgical patients with risk of awareness (bispectral index versus clinical signs)

Outcome: 1 Incidence of awareness (%)

Study or subgroup	Bispectral Index n/N	Clinical Signs n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Myles 2004	2/1225	11/1238		88.9 %	0.18 [0.04, 0.82]
Puri 2003	0/14	1/16		11.1 %	0.36 [0.01, 9.47]
Total (95% CI)	**1239**	**1254**		**100.0 %**	**0.20 [0.05, 0.79]**
Total events: 2 (Bispectral Index), 12 (Clinical Signs)					
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² =0.0%					
Test for overall effect: Z = 2.30 (P = 0.021)					

APPENDICES

Appendix 1. MEDLINE SilverPlatter

#1 explode "Electroencephalography-" / all SUBHEADINGS in MIME,MJME,PT
#2 "Monitoring-Physiologic" / all SUBHEADINGS in MIME,MJME,PT
#3 (intra?operativ* near monitoring) or (intra?operativ* and monitoring)
#4 intra?operativ* near patient
#5 BIS or bispectral*
#6 (bispectral near index*) or (bispectral and index*)
#7 electro?encephalograph*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 ("Anesthesia-and-Analgesia" / all SUBHEADINGS in MIME,MJME,PT) or ("Anesthesia-" / all SUBHEADINGS in MIME,MJME,PT)
#10 (explode "Anesthetics-General" / all SUBHEADINGS in MIME,MJME,PT) or(explode "Anesthesia-General" / all SUBHEADINGS in MIME,MJME,PT)
#11 an?esth* in TI, AB
#12 explode "Postoperative-Period" / WITHOUT SUBHEADINGS in MIME,MJME,PT
#13 #9 or #10 or #11 or #12
#14 #8 and #13
#15 CLINICAL-TRIAL in PT
#16 randomized in AB
#17 placebo in AB
#18 (clinical trials) in MESH
#19 randomly in AB
#20 trial in TI
#21 #15 or #16 or #17 or #18 or #19 or #20
#22 TG=animals
#23 TG=humans

#24 #22 not (#22 and #23)
#25 #21 not #24
#26 #14 and #25
#27 #26 and (PY>1990)

Appendix 2. EMBASE Silver Platter

#1 explode ELECTROENCEPHALOGRAPHY/all subheadings
#2 "patient-monitoring" / all SUBHEADINGS in DEM,DER,DRM,DRR
#3 (intra?operativ* near monitoring) or (intra?operativ* and monitoring)
#4 electro?encephalograph*
#5 explode "bispectral-index" / all SUBHEADINGS in DEM,DER,DRM,DRR
#6 (bispectral near index*) or (bispectral index*)
#7 #1 or #2 or #3 or #4 or #5
#8 explode "general-anesthesia" / all subheadings
#9 explode "anesthetic-agent" / all subheadings
#10 an?esthe*
#11 #8 or #9 or #10
#12 #7 and #11
#13 "RANDOMIZED-CONTROLLED-TRIAL"/all subheadings
#14 "RANDOMIZATION"/all subheadings
#15 "CONTROLLED-STUDY"/all subheadings
#16 "MULTICENTER-STUDY"/all subheadings
#17 "PHASE-3-CLINICAL-TRIAL"/all subheadings
#18 "PHASE-4-CLINICAL-TRIAL"/all subheadings
#19 "DOUBLE-BLIND-PROCEDURE"/all subheadings
#20 "SINGLE-BLIND-PROCEDURE"/all subheadings
#21 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB
#23 (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)
#24 #21 or #22 or #23
#25 HUMAN in DER
#26 (ANIMAL or NONHUMAN) in DER
#27 #25 and #26
#28 #26 not #27
#29 #24 not #28
#30 #12 and #29
#31 #30 and (PY > 1990)

Appendix 3. CENTRAL

#1 MeSH descriptor Electroencephalography explode all trees
#2 MeSH descriptor Monitoring, Physiologic, this term only
#3 intraoperative monitoring
#4 intraoperative near (patient* or monitoring)
#5 BIS or bispectral*
#6 bispectral near index*
#7 bispectral index*
#8 electroencephalograph*
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Anesthesia and Analgesia explode all trees
#11 (anaesth* or anesth*):ti,ab
#12 MeSH descriptor Postoperative Period, this term only

#13 (#10 OR #11 OR #12)
#14 (#9 AND #13)

WHAT'S NEW

Last assessed as up-to-date: 13 August 2007.

7 August 2008	Amended	Minor edits to text

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 4, 2007

10 January 2008	Amended	Converted to new review format.
14 August 2007	New citation required and conclusions have changed	Substantive amendment
14 August 2007	Amended	We changed the search strategy for MEDLINE, EMBASE and CENTRAL

CONTRIBUTIONS OF AUTHORS

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Co-ordinating the review: YP

Undertaking manual searches: YP, Aram Phongchiewboon (AP) and Nutchanart Boonjeungmonkol (NB)

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Organizing retrieval of papers: YP

Screening retrieved papers against inclusion criteria: YP and NB

Appraising quality of papers: YP, AP and NB

Abstracting data from papers: YP and NB

Writing to authors of papers for additional information: YP

Providing additional data about papers: YP and NB

Obtaining and screening data on unpublished studies: YP

Data management for the review: YP

Entering data into Review Manager (RevMan 4.2): YP and NB

RevMan statistical data: YP

Other statistical analysis not using RevMan: YP

Double entry of data: data entered by person one YP; data entered by person two NB

Interpretation of data: YP

Statistical analysis: YP

Writing the review: YP

Securing funding for the review: YP

Performing previous work that was the foundation of the present review:YP

Guarantor for the review (one author): YP

Responsible for reading and checking review before submission: YP

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthesia Recovery Period; *Electroencephalography; Anesthesiology [methods; organization & administration]; Anesthetics [*administration & dosage]; Monitoring, Intraoperative [*methods]

MeSH check words

Humans