Original Article

Effect of bispectral index on intra-operative awareness: A meta-analysis of randomized controlled studies

ABSTRACT

Background: Randomized controlled trials (RCTs) investigating the efficacy of bispectral index (BIS) to reduce intra-operative awareness (IOA) have reported conflicting results. The purpose of this meta-analysis is to consolidate results from RCTs to assess the efficacy of BIS in reducing IOA when compared to controls. Secondary outcomes included time to extubation, time to spontaneous and/or verbal eye opening, PACU discharge time, and utilization of inhaled anesthetics.

Methods: RCTs which reported on one of the primary and/or secondary outcomes were included. Literature search utilized keywords "randomized control trial" and "intraoperative awareness." Meta-analysis was performed using RevMan 5.

Results: Twenty-seven RCTs were included in the study with a total of 35,585 patients, with 18,146 patients in the BIS and 17,439 in the control group. Eighteen of 14,062 patients (0.12%) and 42 of 16,765 (0.25%) reported definite IOA in the BIS and control group, respectively, with no statistically significant difference. BIS was effective in reducing the time to spontaneous eye opening by an average of 1.3 minutes and the time to extubation by an average of 1.97 minutes. There was no difference in PACU discharge times among the groups. There was a significant decrease in consumption of sevoflurane but no difference in desflurane and propofol compared to the control group.

Conclusion: While BIS monitoring results in decreased incidence of intra-operative awareness by half, it was not statistically significant. BIS provides modest benefits with regard to reducing the time to extubation, the time to spontaneous eye opening, and consumption of sevoflurane.

Level of evidence: I.

Key words: Anesthesiology, intra-operative awareness, meta-research

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Introduction

Intra-operative awareness (IOA) is a distressing complication with the reported incidence between 0.1 and 0.2% for patients undergoing general surgery,[1,2] increasing up to 1% in high-risk procedures.[3,4] In the United States, approximately 20,000 to 40,000 patients experience awareness every year.[5,6] Classically, somatic (motor response and respiratory patterns) and autonomic (blood pressure, heart rate, lacrimation, sweating) signs, along with monitoring of minimum alveolar concentration (MAC) of the inhaled anesthetic, have been used in the assessment of the depth of anesthesia. With the development of newer technologies, a number of intra-operative monitoring methodologies have been introduced to help the clinic assess the depth of anesthesia, all with the goal of preventing of IOA.[7]

The bispectral index (BIS) utilizes the synchronicity of electroencephalographic (EEG) readings to estimate the depth of anesthesia. BIS values range from 0 to 100, with 0 indicating a suppression of electrical brain activity and 100 indicating an awake state; values between 40 and 60 have been recommended to provide a sufficient depth of hypnosis in order to prevent awareness during surgery and post-operative recall.[8] Additionally, it can be rationalized that by more accurately measuring the depth of anesthesia, the quantity of anesthetic medication delivered can therefore be minimized, which may reduce hemodynamic changes from deep anesthesia, reduce incidence of anesthetic side effects, decrease the extubate time, and hasten recovery.[9]

Since the BIS algorithm first entered commercial use in 1994, numerous randomized control trials (RCTs) have investigated its efficacy, measuring endpoints such as reducing IOA,[10] incidence of relevant adverse events such as anesthetic-induced neurotoxicity,[11] post-operative pain,[12] and intensive care unit (ICU) time following surgery.[13] However, RCTs have reported conflicting results when compared to a control group with respect to reduction of IOA.[5,14] Furthermore, the effectiveness of BIS monitoring on outcomes such as improved recovery times and reduction of anesthetic agents required to maintain hypnosis[15,16] have reported conflicting results as well. The primary aim of this meta-analysis was to consolidate data from RCTs to evaluate the efficacy of BIS monitoring in reducing IOS compared to the control group. Secondary outcomes investigated the effect of BIS on time to verbal response, motor response, and extubation; post-anesthesia care unit stay; amount anesthetic medication; and agents used when compared to control.

Materials and Methods

This meta-analysis was performed according to the guidelines published by PRISMA and the Cochrane Collaboration. The study did not involve human and/or animal subjects and did not require institutional review board approval.

Literature search

Two authors independently conducted systematic reviews of the MEDLINE, EMBASE, science citation index, Cochrane Central Register of Controlled Trials, and Google Scholar databases to identify studies published before February 15, 2019. Keywords included "Bispectral index" and "Randomized controlled studies". Only studies in English were included. No date restriction was applied.

Study selection

All published studies involving RCTs which investigated the benefit of BIS when compared to a control with respect to intra-operative awareness (possible and definite); time to verbal response, motor response, and extubation; post-anesthesia care unit stay; or amount anesthetic medication used were included. Only studies involving general anesthesia were included. Studies involving sedation and patients less than 18 years were excluded. Meeting or conference abstracts were excluded. Eligibility assessment was performed independently by two reviewers. Disagreements between reviewers were resolved by consensus. Only publications in English were included.

Validity assessment

To ascertain validity of included studies, assessment was done by two reviewers independently. Disagreements between reviewers were resolved by consensus. Jadad scoring [Table 1]

Table 1: Jadad scoring of risk of bias of RCSs

Randomization
Was the study described as randomized (this includes words such as randomly, random, and randomization)? (+1 Point)
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? (+1 Point)
Blinding
Was the study described as double blind? (+1 Point)
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)? (+1 Point)
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc)
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).
Withdrawals
Was there a description of withdrawals and dropouts? (+1 Point)

was used for assessment of quality of study. The quality of an individual study was classified into the below category based on cumulative scores from each question.

High quality: 4–5

Medium quality: 2–3

Low quality: 0–1.

Data collection and extraction

Two authors independently extracted data from each study using a modified Cochrane data extraction sheet. Disagreements were resolved by consensus. Information extracted from each study included the following: 1. study characteristics including sample size, study design, inclusion BIS criteria, and limitations; 2. events of intra-operative awareness (definite and possible); time to verbal response, motor response, or extubation; post-anesthesia care unit stay; amount of anesthetic medication; or agents used.

Statistical methods and analysis

The meta-analysis was performed with RevMan 5 software. Pooled risk estimate analysis was performed using the random-effect model. Heterogeneity was assessed by funnel plot, I2, and Chi-square value. A *P*-value <0.05 and I2 >50% were considered suggestive of statistical heterogeneity. Pooled odds ratio (pOR) with 95% confidence interval (CI) was used to assess the efficacy. Studies which did not report on useable data, that is, mean, standard deviation, and/or standard error, were excluded.

Results

A flowchart of the search strategy is shown in Figure 1. Twenty-seven RCTs were included in the comparison between BIS and the control group. Study characteristics are described in Table 2, with available data included. There were a total of 35,585 patients, with 18,146 patients in the BIS and 17,439 in the control group. Primary outcomes included incidence of definite awareness in six studies[5,8,10,17-19]; possible and definite awareness[5,8,10,17,19]; time to spontaneous eye opening[20-29]; time to extubation[18,20-28,30-34]; time to discharge from PACU[18,20-28,30-33]; and consumption of sevoflurane[18,20,21,26,32-37], isoflurane, desflurane[22,27,28,31,32], and propofol.[24,28,30,31,38,39] Study characteristics including year of study, country, inclusion and exclusion criteria, and limitations are described in Table 2.

Quality assessment

Jadad scores of included studies are shown in Table 1. Jadad scores of the 27 RCTs varied between 3 and 5. Twenty studies had low risk of bias, and seven had medium-risk bias. Sample sizes of the studies ranged from 20 to 18,836, with an average sample size of 1203 per study.

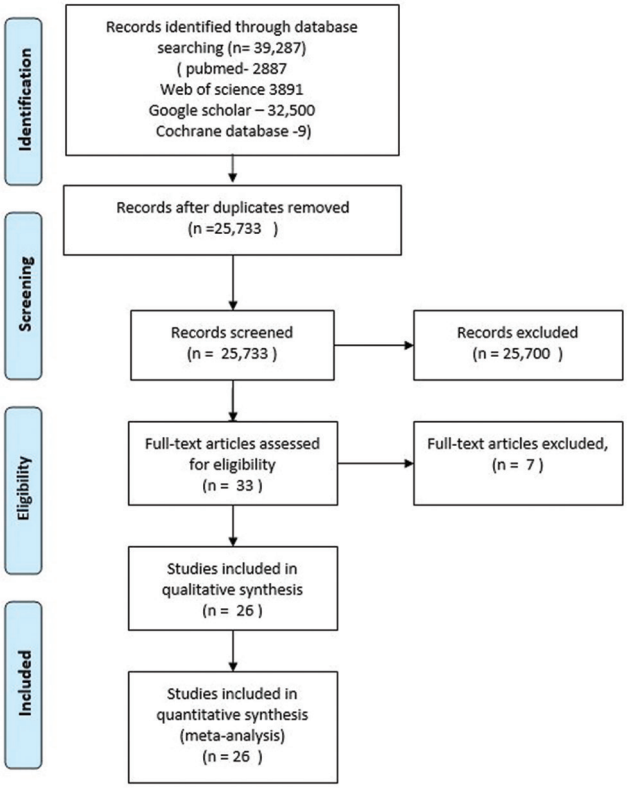

Figure 1: Prisma flow diagram of literature search strategy

Effect of intra-operative awareness

Definite awareness

Six studies[5,8,10,17-19] comprising 30,827 patients reported on incidence of definite IOA. Eighteen of 14,062 patients (0.12%) and 42 of 16,765 (0.25%) reported definite IOA in the BIS and control group, respectively. Incidence of definite IOA was twice in the control group when compared to the BIS group; however, there was no statistically significant difference among the two groups [OR = 0.50; 95% CI (0.19, 1.27); $P = 0.06$; $I^2 = 52\%$] [Figure 2a]. Sub-analysis of the four studies[5,8,17,18] (n = 23,136) which used an inhalational anesthetic showed no statistical significance [OR = 0.95; 95% CI (0.31, 2.89); $P = 0.21$; $I^2 = 34\%$] in definite IOA between the BIS and control groups. Among the two studies[10,19] which used intravenous anesthesia, 6/4144 (0.1%) in the BIS cohort and 26/3547 (0.7%) controls experienced IOA, which was statistically significant [OR = 0.20; 95% CI (0.08, 0.49); $P < 0.001$; $I^2 = 0\%$].

Definite and possible awareness

Data from five studies[5,8,10,17,19] (n = 30,797) did not suggest a difference in incidence of definite and possible awareness between the BIS and control cohorts [OR = 0.83;

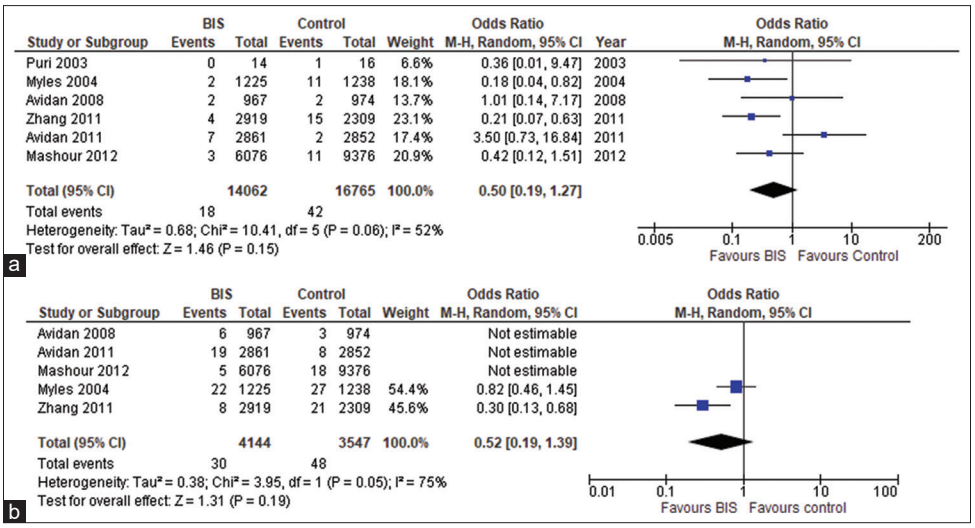

Figure 2: Forest plot showing the effect of bispectral index on definite intra-operative awareness (a) and possible and definite intra-operative awareness (b) compared to controls

95% CI (0.39, 1.78); $P = 0.64$; $I^2 = 74\%$] [Figure 2b]. Sub-analysis of the three studies[5,8,17] (n = 23,136) which used an inhalational anesthetic showed no statistical significance (OR = 1.25; 95% CI [0.40, 3.97]; $P = 0.70$; $I^2 = 72\%$) between the BIS and control groups. Among the two studies[10,19] which used intravenous anesthesia, there was no statistical significance among the groups with regard to the outcome (OR = 0.52; 95% CI [0.19, 1.39]; $P = 0.19$; $I^2 = 75\%$).

Effect on peri-operative outcomes

There were modest benefits with the use of BIS compared to controls with respect to time to spontaneous eye opening in the nine studies which reported on the outcome by an average of 1.3 minutes[20-29] (n = 703; MD = -1.3; 95% CI [-2.28, -0.32]; $P = 0.01$; $I^2 = 81\%$) [Figure 3a]. Funnel plot did reveal a publication bias. Data from the 14 studies[18,20-28,30-33] show a modest benefit on time to extubation in the BIS groups by an average of 1.97 minutes (n = 983; MD = -1.97; 95% CI [-2.83, -1.11]; $P < 0.01$; $I^2 = 75\%$) [Figure 3b]. Funnel plot did show a publication bias. There was no difference in PACU discharge times among the groups[18,20-28,30-34] (n = 496; MD = -3.73; 95% CI [-9.04, 1.58]; $P = 0.17$; $I^2 = 76\%$) [Figure 3c].

Effect on utilization of anesthetics

There was a statistically significant reduction in sevoflurane utilization in the BIS group compared to controls (nine studies[18,20,21,26,32-37]; n = 504; SMD = -0.37; 95% CI [-0.68, -0.06]; $P = 0.02$; $I^2 = 65\%$) [Figure 4a]. There was a no significant reduction in desflurane utilization among the cohorts (five studies[22,27,28,31,32]; n = 352; SMD = -0.52; 95% CI [-1.24, 0.19]; $P = 0.15$; $I^2 = 90\%$) [Figure 4b]. There was only one study which reported on isoflurane consumption, which concluded that there was a benefit with the use of BIS. There was a no significant reduction in propofol consumption in the BIS group compared to controls (six studies[24,28,30,31,38,39]; n = 300; SMD = -0.83; 95% CI [-1.71, 0.04]; $P = 0.06$; $I^2 = 90\%$) [Figure 4c].

Discussion

The results of this meta-analysis showed there was a twofold decrease in definite intra-operative awareness with the use of BIS when compared to controls. However, this reduction did not reach statistical significance. With respect to peri-operative outcomes, there were modest benefits with the use of BIS compared to controls with respect to time to spontaneous eye opening by an average of 1.3 minutes and time to extubation by 1.97 minutes. There was no benefit on time to discharge from PACU. There was a reduction in sevoflurane but not desflurane or propofol with the use of BIS.

The results of this meta-analysis are different with a previous meta-analysis by Gao *et al*.[40] Our meta-analysis included one additional study with a small sample size of 30 among patients undergoing cardiac surgery. Furthermore, for incidence of IOA, data from the *post hoc* analysis were included from Mashour *et al*. study.[8] In this study, incidence of IOA in the no intervention group was not included in the BIS group. This resulted in only 3/6076 (0.05%) in the BIS group, as opposed to 8/9460 (0.08%) used by Gao *et al*.[40] These differences resulted in the twofold decrease in incidence of IOA in the BIS cohort compared to controls, trending toward statistical significance ($P = 0.06$). We did not perform a sub-analysis of outcomes among inhalational anesthesia and total intravenous anesthesia as this would have further

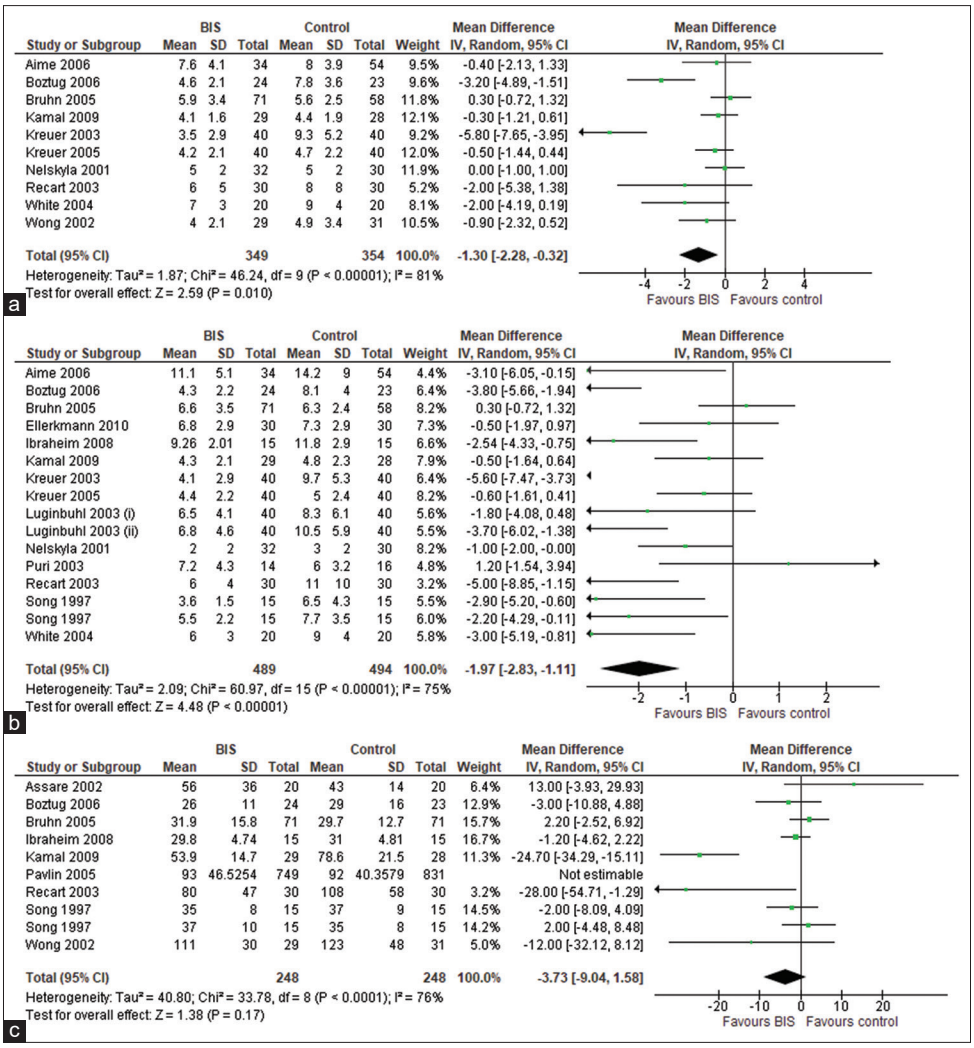

Figure 3: Forest plot showing the effect of bispectral index on spontaneous eye opening (a), time to extubation (b), and time to discharge from PACU (c) compared to controls

decreased the number of studies included in each outcome. Gao *et al*.[40] showed a lower incidence of intra-operative awareness with BIS in patients with intravenous anesthesia when compared to controls in the two studies included. They also did not find a significant difference in the incidence of intra-operative awareness between BIS and control groups in patients with inhalation anesthesia in the three studies they included.

Previous meta-analyses have shown that BIS reduced the time to eye opening by an average of 1.3 minutes[41,42] and the time to extubation by 2.5–2.6 minutes.[41,42] These data collaborate findings of our study as well. The modest difference in time to extubation may be attributed to exclusion of studies reporting outcomes as median, inclusion of additional studies, and difference in statistical software used.

Punjasawadwong *et al*. reported the time to discharge from PACU by an average of 6.75 minutes in the BIS cohort. However, both the meta-analyses by Chiang *et al*.[41] and our study did not reveal any benefit regarding time to discharge from PACU.

Punjasawadwong *et al*. concluded that there was a reduction in anesthetic requirement of sevoflurane, isoflurane, desflurane, and propofol. Our study showed reduced anesthetic requirement with the use of BIS with respect to sevoflurane but not with desflurane or propofol. There was only one study which investigated the benefit of BIS of reduction of isoflurane requirement. Thus, any meaningful conclusion to its efficacy will be limited by sample size. However, our study was unable to quantify the amount of reduction in anesthetic utilization due to the difference in reported outcome measures in the different studies. For quantification of anesthetic requirement, Punjasawadwong *et al*.[42] converted the end tidal concentrations of volatile anesthetics into minimal alveolar concentration (MAC) equivalents, standardized to both age and duration. While

Table 2: Study characteristics, limitations and Jadad scores of included studies

Study	Yr.	Country	Sample size (M/F)		Mean Age	
			BIS	Ctrl	BIS	Ctrl
Ahmad, S.	2003	United States	49 (?/?)	48 (?/?)	35.6±8.7	35.4±8.9
Aime, I.	2006	France	54 (23/33)	34 (14/20)	54±15	57±19
Avidan, M.	2008	United States	967 (516/451)	974 (523/451)	59.5±14.8	59.2±14.6
Avidan, M.	2011	United States	2861 (1621/1240)	2852 (1679/1173)	60±14.2	61±14.4
Assare, H.	2002	Sweden	20 (??/??)	20 (??/??)	45±14	44±11
Basar, H.	2003	Turkey	30 (17/13)	30 (18/12)	42.1±3.3	39±4.5
Boztug, N.	2003	Turkey	24 (11/13)	23 (12/11)	45±11	50±10
Bruhn, J.	2005	Germany	71 (?/?)	71 (?/?)	48.6±15	46.3±13
Ellerkman, R.K.	2010	Germany	27 (9/18)	27 (12/15)	50.6±15.7	53.6±18.4
Ibraheim, O.	2006	Saudi Arabia	15 (9/6)	15 (11/4)	39±4.5	41.21±5.07
Kamal, N.	2009	Egypt	29 (18/11)	28 (20/8)	51.6±7.4	52.1±5.2
Kreuer, S.	2003	United States	40 (20/20)	40 (20/20	43.8±4.2	46.1±14.5
Kreuer, S.	2005	Germany	71 (?/?)	71 (?/?)	48.6±15	46.3±13
Luginbh, M.	2003	Switzerland	40 (0/40) (desflurane) 40 (0/40) (propofol)	40 (?/?) (desflurane) 40 (?/?) (propofol)	45.2±17.5 (desflurane) 46.3±15.4 (propofol)	47.1±17.8 (desflurane) 48.7±15.7 (propofol)
Mashour, G.	2012	United States	9460 (?/?)	9376 (?/?)	N/A	N/A
Muralidhar, K.	2008	India	10 (9/1) (isoflurane) 10 (8/2) (propofol)	10 (8/2) (isoflurane) 10 (10/0) (propofol)	50±6 (isoflurane) 52±7 (propofol)	50±4 (isoflurane) 47±5 (propofol)
Myles, P.S.	2004	Australia	1225 (752/473)	1238 (784/454)	58.1±16.5	57.5±16.9
Nelsekya, K.	2001	Finland	32 (0/32)	30 (0/30)	32±6	32±6
Puri, G.D.	2003	India	14 (?/?)	16 (?/?)	38.25±14.02	32.08±13.84
Recart, A.	2003	United States	30 (9/21)	30 (10/20)	47±17	46±15
Samarkandi, A.	2006	Saudi Arabia	20 (?/?)	20	12-Feb	12-Feb
Song, D.	1997	United States	15 (0/15) (desflurane) 15 (0/15) (sevoflurane)	15 (0/15) (desflurane) 15 (0/15) (sevoflurane)	28±4 (desflurane) 26±6 (sevoflurane)	27±6 (desflurane) 26±7 (sevoflurane)
Struys, M.	2001	United States	10 (0/10)	10 (0/10)	42±8	46±6
White, P.	2004	United States	20 (?/?)	20 (?/?)	54±14	48±10
Wong, J.	2001	Canada	29 (19/10)	31 (21/10)	71±5	70±6
Zhang, C.	2011	China	2893 (1237/1656)	2280 (971/1309)	46.95±14.86	46.06±14.59
Zohar, E.	2006	Israel	25 (21/4)	25 (22/3)	73±8	76±7

Study	Inclusion criteria	Exclusion criteria	BIS criteria	Limitation	Jadad score
Ahmad, S.	Gynecologic laproscopy, ASA status I/II	None	50-60	No blinding	3
Aime, I.	Adults (18-80) with ASA physical status I/II/III undergoing elective abdominal, gynecologic, urologic, or orthopedic surgery <1 h	History of disabling central nervous or cerebrovascular disease, hypersensitivity to opioids, substance abuse, treatment with opioids or psychoactive medications, body weight <70% or >130% of ideal	40-60	Difference in baseline demographics learning contamination bias poor adherence to protocol, postoperative anesthetic use	3
Avidan, M.	Patients with at least 1 of the following major risk factors: long-term use of anticonvulsants/ opiate/benzodiazepines, cocaine, cardiac ejection fraction <40%, history of anesthesia awareness, history of difficult intubation, ASA physical status class 4 or 5, aortic stenosis, end-stage lung disease, marginal exercise intolerance, pulmonary hypertension, planned open-heart surgery, daily alcohol consumption; or, 2+minor criteria: previous use of beta-blockers, chronic obstructive pulmonary disease, obesity with BMI >30	Surgery requiring a wake-up test or patient orientation which prevented BIS attachment, dementia, inability to provide informed consent, history of stroke with residual neurological deficits	40-60	false memories during awareness interviews, subjectivity in diagnosing awareness	3

Contd...

Table 2: Contd...

Study	Inclusion criteria	Exclusion criteria	BIS criteria	Limitation	Jadad score
Avidan, M.	Adults (18+) undergoing surgery at high risk for intraoperative awareness with at least 1 risk factor (planned open heart surgery, aortic stenosis, pulmonary hypertension, opiate/benzodiazepine/anticonvulsant use, daily alcohol consumption, ASA status 4, end-stage lung disease, history of difficult intubation, cardiac ejection fraction <40%, marginal exercise tolerance)	Dementia, inability to provide written consent, history of stroke with residual neurological defects	BIS between 40-60	desentization of physician to alarms, missing data affecting rare results due to patient death	5
Assare, H.	Elective daytime knee arthroscopy, ASA status I/II	ASA >3	60	Difference in physician expertise/comfort for titrating using BIS, lack of requirement for muscle relaxation, small sample size	2
Basar, H.	Open abdominal surgery, ASA status I/II	Renal, hepatic, or neurological dysfunction, use of benzodiazepenes, anticonvulsants, alcohol, opiods, or other psychotropic drugs	40-60	Lack of double blinding	2
Boztug, N.	Adults (18-75) undergoing supratentorial craniotomy	Any medications with known CNS or cardiopulmonary interactions, need for postoperative ventilation	40-60	sample size	5
Bruhn, J.	Adults (18-80) undergoing minor surgery expected to last at least 1 hour	History of disabling central nervous or cerebrovascular diseases, hypersensitivity to opiods or substance abuse, treatment with opiods or psychoactive medications	50-60	sample size	4
Ellerkman, R.K.	Adult (18-80) patients underoing minor orthopedic surgery expected to last at least 1 hour, ASA status I/II/III	History of disabling central nervous or cerebrovascular diseases, hypersensitivity to opiods or substance abuse, treatment with opiods or psychoactive medications	40-60	Inclusion of multiple surgery types confounding results, localized anesthesia blocking pain perception measured during general anesthesia in study	5
Ibraheim, O.	Morbidly obese (BMI >35) patients undergoing gastric banding, ASA status I/II	Renal, hepatic, or neurologic dysfunction, use of benzodiazepenes, anticonvulsants, alcohol, opiods, or other psychotropic drugs	40-60	Lack of double blinding, differences in experience between administering residents	2
Kamal, N.	Patients undergoing elective abdominal surgery of duration at least 2 hours	History of disabling central nervous/cerebrovascular disease, opioid hypersensitivity, history of substance abuse, treatment with opioids/psychoactive medications, BMI>40	BIS between 50-60	Variation in physician timing of reducing anesthetic drugs at end of surgery	4
Kreuer, S.	Adults (18-80) with ASA physical status I/II/III undergoing minor orthopedic surgery expected to last at least 1 hour	History of disabling central nervous or cerebrovascular diseases, hypersensitivity to opioids or substance abuse, treatment with opioids or any psychoactive medications	40-65	Investigator bias in standard practice group, learning contamination bias, sex difference in recovery from propofol infusion	4
Kreuer, S.	Adults (18-80) with ASA status I/II/III undergoing minor surgeries expected to last at least 1 hour, prospective	History of disabling central nervous or cerebrovascular diseases, hypersensitivity to opioids or substance abuse, treatment with opioids or any psychoactive medications	40-60	Learning contamination bias, lack of blinding giving investigator bias, lower average BIS value than previous studies, difficulties maintaining same BIS value between control groups, use of desflurane-remifentanil instead of desflurane-fentanyl lowered recover times and reduced differences	4

Contd...

Table 2: Contd...

Study	Inclusion criteria	Exclusion criteria	BIS criteria	Limitation	Jadad score
Luginbh, M.	Scheduled gynecological surgery expected to last>15 minutes	ASA >3, history of CNS diseases, currently taking EEG-affecting drugs	40-60	Pharmacodynamic variation in desflurane for measuring desflurane concentrations	4
Mashour, G.	Adults (18+) receiving inhaled or intravenous anesthesia for any surgical cases not involving the forehead, and available for follow-up interviews	Intracranial procedure, adhesive allergy, psychosis, history of traumatic brain injury	40-60	Insufficient patient number to discern to what extent BIS is able to prevent definitive awareness due to rarity of the event, proportion of patients randomized to BIS protocol but failed to receive BIS monitoring due to technical limitations	4
Muralidhar, K.	Coronary artery bypass graft	Requirement of extra-corporeal circulation electively or during course of surgery, poor left ventricular function (ejection fraction<40%), LV aneurysms, requirement of intra-aortic balloon pump, hepatic or renal dysfunction, presence of unstable angina, carotid stenosis, cerebrovascular accident, drug or alcohol abuse	45-55	Insufficient sample size to determine intraoperative awareness, limited to low-risk patients with good LV function	3
Myles, P.S.	Adults (18+) undergoing surgery with at least 1 of the following risk factors: caesarean section, high-risk cardiac surgery (ejection fraction<30%, cardiac index<2 L/min/m ^ 2, severe aortic stenosis, pulmonary hypertension, off-pump coronary bypass surgery), acute trauma with hypovolemia, rigid bronchoscopy, significantly impaired cardiovascular status with expected intraoperative hypotension requiring treatment, severe end-stage lung disease, past history of awareness, anticipated difficult intubation where an awake intubation technique was not planned, known or suspected heavy alcohol intake, chronic benzodiazepine or opioid use, or current protease inhibitor therapy	Inadequate comprehension of English, traumatic brain injury, memory impairment, psychosis, suspected electroencephalograph abnormality (epilepsy, previous brain resection or scarring), unavailability for postoperative interview	40-60	Routine care control patients being exposed to higher levels of midazolam and propofol due to increased concern for awareness, delaying recover, variations between anesthesiologists in reducing drug administration at end of surgery, vagueness of intraoperative dreaming and measuring possible awareness	5
Nelsekya, K.	Women (18-50) with ASA status I/II and normal body weight (BMI 20-27) undergoing gynecologic laproscopy	N/A	50-60	Capacity to void as a requirement for home-readiness has been questioned, drain in peritoneal cavity not routine for diagnostic laproscopy, lowered threshold of admission for patients due to free first overnight stay,	4
Puri, G.D.	Adults (18-70) undergoing cardiopulmonary bypass	Known neurological disorders, poor ventricular function (ejection fraction <40%), NYHA Grade IV, diabetes mellitus, impaired renal or hepatic function	45-55	Multiple non-anesthesia factors determining time and success of tracheal extubation for bypass procedure, hemodilution of anesthetic drugs, neurotransmitter blockade effect on ability to respond following 4 twitch recover, practitioner learning	5
Recart, A.	General laproscopic surgery	History of CNS disease, chronic use of psychoactive medication, clinically significant cardiovascular, renal, hepatic, endocrinologic disorders	45-55	Interference of simultaneous application of AEP+BIS electrode, insufficient power for adverse events, limited diversity of patients	4

Contd...

Table 2: Contd...

Study	Inclusion criteria	Exclusion criteria	BIS criteria	Limitation	Jadad score
Samarkandi, A.	Children (2-12) undergoing elective below umbilical surgery for repair of hypospadias or orchidopexy expected to last >45 min, ASA status I/II	Mandatory preoperative sedation, mental diseases, epilepsy, history of developmental delay, medication affecting CNS, contraindication to inhalation anesthetics, improper caudal anesthesia causing a >20% rise vs. basal heart rate or blood pressure	40-60	Nonconstant CO2 and temperature changes between children, all anesthesia delivered by a single provider	4
Song, D.	Women undergoing laproscopic tubal ligation, ASA status I/II	Known neurologic, cardiovascular, or renal disease, impaired renal or hepatic function, body weight more than 100% above ideal, history of drug or alcohol abuse	45-60	Insufficient sample size to rule out incidence of intraoperative recall with reduced dosage of anesthetics, no double blinding	4
Struys, M.	Women undergoing gynecologic laparotomy, ASA status I/II	None	50-60	30s delay in BIS calculations in a closed-loop system,	3
White, P.	Gynecologic laproscopic surgery, ASA status I/II/III	Known neurological or psychiatric disorders, anticonvulsant or centrally active medications, clinically significant cardiovascular, respirator, hepatic, renal, or metabolic disease, long term drug/alcohol use, body weight>50% of ideal	50-60	Investigator bias from previous familiarity with BIS usage, potential for more rigorous blinding procedures, inadequate power to detect adverse events	4
Wong, J.	Adults (60+) undergoing elective orthopedic knee or hip replacement, ASA status I/II/III	Significant cardiorespiratory or end-organ disease, depression or psychiatric disorders, dementia, previous cerebrovascular accident, head trauma, inadequate command of English, drug or alcohol abuse, MMSE score<24 on day of surgery	50-60	Insufficient sensitivity of MMSE to detect experimental-caused mild cognitive deficits, learning from repeated testing, postoperative morphine confounding differences on tests, inadequate sample size and power to detect postoperative dysfunction	5
Zhang, C.	Adults (18+) without apparent mental defects undergoing scheduled total intravenous anesthesia that gave informed consent	Unavailable for interviews post-surgery, inability to speak Mandarin Chinese, under awake intubation, undergoing intraoperative arousal test	40-60	Patient variation in surgical history, ASA status, and surgery types, lack of scheduled obstetric surgeries, anesthetic dreaming clouding recall	5
Zohar, E.	Geriatric (65+) patients undergoing elective short transurethral surgery	History of unstable cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic diseases	50-60	Shortened duration of surgical procedures, sevoflurane-sparing effects of nitrous oxide, differing amounts of fentanyl given to groups, insufficient sensitivity of neurological testing to detect early recovery following anesthesia	4

advantageous in estimation of quantity of the anesthetic required, these assumptions decrease accuracy of results. In our study, we used mean difference instead of standardized mean difference. Also, outcome data reported as mean and range were not included. This provided more accurate data at the cost of quantification of data. This may account for the difference in results with our study.

Recent studies have also reported on additional benefits with BIS-guided anesthesia, including reduced post-operative delirium and improved cognitive function.[42-44] Our study investigated the benefit of BIS in the setting of general anesthesia patients.

A Cochrane review published in 2018[45] investigated the clinical impact and resource utilization of BIS monitoring versus clinical assessment for sedation in mechanically ventilated adults in the ICU. The findings, though uncertain due to the low quality of evidence from the included studies, concluded that there was insufficient evidence about the effects of BIS monitoring for sedation in critically ill mechanically ventilated adults on clinical outcomes or resource utilization. Furthermore, while Bocskai *et al*.[46] demonstrated that the use of BIS and train-of-four monitoring decreased the total cost of anesthesia drugs and hastened post-operative recovery, these were associated with higher disposable costs. The cost efficacy of BIS remains inconclusive.

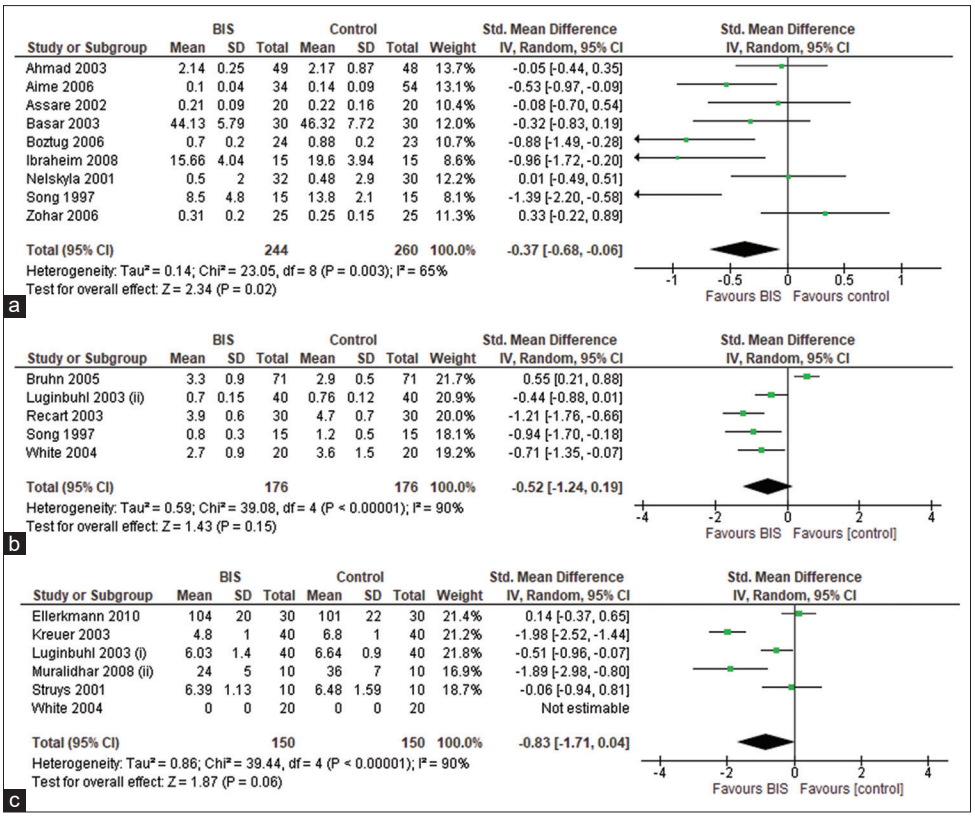

Figure 4: Forest plot showing the effect of bispectral index on sevoflurane (a), desflurane (b), and propofol (c) consumption compared to controls

The results of our study should be interpreted understanding the inherent limitations to any meta-analysis. There was high heterogeneity among studies, and the random-effect model was used in all analyses to account for heterogeneity and publication bias. Several studies were excluded due to lack of usable reported data. All the limitations of the included studies should be considered as well. Furthermore, while the Jadad scoring for risk of bias is among the most widely used tools for assessment of methodological quality, interpretation of bias should be done with an understanding of the limitations of this scoring scale. Due to lack of consistency with respect to amount of anesthetic requirement reported among studies, quantification of reduction of anesthetic requirement was not done.

Conclusion

The overall incidence of definite IOA was 0.12% and 0.25% in the BIS and control group, respectively, with no statistically significant difference. BIS was effective in reducing the time to spontaneous eye opening by an average of 1.3 minutes and the time to extubation by an average of 1.97 minutes. There was no difference in PACU discharge times among the groups. There was a significant decrease in consumption of sevoflurane but no difference in desflurane and propofol compared to the control group. The risk of bias of the study was low–medium.

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Conflicts of interest

There are no conflicts of interest.

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