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Processed Electroencephalogram Monitoring and Postoperative Delirium: A Systematic Review and Meta-Analysis

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Abstract

Background—Postoperative delirium complicates approximately 15%–20% of major operations in patients ≥ 65 years and is associated with adverse outcomes and increased resource utilization. Furthermore, patients with postoperative delirium might also be at risk of developing long-term postoperative cognitive dysfunction. One potentially modifiable variable is use of intraoperative processed electroencephalogram to guide anesthesia. This systematic review and meta-analysis examines the relationship between processed electroencephalogram monitoring and postoperative delirium and cognitive dysfunction.

Methods—A systematic search for randomized controlled trials was conducted using Ovid MEDLINE, PubMed, EMBASE, Cochrane Library, and Google search using the keywords: processed electroencephalogram, bispectral index, postoperative delirium, postoperative cognitive dysfunction. Screening and data extraction were conducted by two independent reviewers and risk of bias was assessed. Postoperative delirium combined-effect estimates calculated with a fixed-effects model were expressed as odds ratios (OR) with 95% confidence intervals (95%CI).

Results—Thirteen of 369 search results met inclusion criteria. Postoperative cognitive dysfunction data were excluded in meta-analysis due to heterogeneity of outcome measurements; results were discussed descriptively. Five studies were included in the quantitative postoperative delirium analysis, with data pooled from 2,654 patients. The risk of bias was low in three studies and unclear for the other two. The use of processed electroencephalogram-guided anesthesia was associated with a 38% reduction in odds for developing postoperative delirium (OR = 0.62; $p<0.001$; 95%CI, 0.51 to 0.76).

Conclusions—Processed electroencephalogram-guided anesthesia was associated with a decrease in postoperative delirium. The mechanism explaining this association however, is yet to

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be determined. Data are insufficient to assess the relationship between processed electroencephalogram monitoring and postoperative cognitive dysfunction.

Introduction

Delirium occurs in approximately 15%–20% of major operations in patients ≥ 65 years of age.[1] Postoperative delirium is associated with prolonged length of stay, increased rates of institutionalization after discharge, mortality, and long-term postoperative cognitive dysfunction. [2] The presence of postoperative delirium increases healthcare expenditure by $16,303 to $64,421 per patient, and the burden of delirium on the health care system ranges from $38 billion to $152 billion per year.[3]

Delirium is a geriatric syndrome with baseline patient vulnerability factors augmented by precipitating risk factors, which include both medical hospitalizations and surgical events. Baseline conditions associated with postoperative delirium include increasing age, pre-existing cognitive impairment, functional impairment, sensory impairment, and institutional residence.[4]

In the surgical population, identification of modifiable, precipitating perioperative factors for postoperative delirium is critical. These include inadequately controlled pain, dehydration, anemia, and electrolyte abnormalities, *etc* [5–7] The type, duration, and depth of anesthesia have come under scrutiny as possible factors contributing to changes in cognition.

There are several United States Food and Drug Administration-approved processed electroencephalogram monitors which are marketed as monitoring depth of anesthesia, with the two most common being the Bispectral Index (BIS) monitor (Medtronic/Covidien, Minnesota) and the SEDline monitor (Masimo Corporation, California). [8] A dimensionless number ({BIS or Patient State Index (PSI}) is calculated ranging from 0, no brain activity, to 100, awake. [9] BIS values between 40 and 60 allow sufficient anesthesia for surgery and prevention of intraoperative awareness; lower processed electroencephalogram values are associated with a deep hypnotic state. [10] Other intraoperative processed electroencephalograms include the GE Datex-Ohmeda Entropy (GE Healthcare, Wisconsin), Narcotrend-Compact M (Narcotrend-Gruppe, Germany) and SNAPII (Everest Biomedical Instruments, Missouri). Another methodology uses evoked electrical activity monitors, such as the A-line monitor (Odense, Denmark), which measures auditory evoked potentials. [11] The algorithms and underlying data for these indices are proprietary and despite their development for guiding anesthesia, their utility is not clearly defined or validated. [12,13]

Whether processed electroencephalogram monitors have consistent perioperative benefits remains to be determined. There is evidence that they reduce anesthetic dose and recovery time Bispectral index but their effect on intraoperative awareness and postoperative recall is controversial. [14,15] A few randomized controlled trials suggest there may be a lower incidence of postoperative delirium as well as postoperative cognitive dysfunction with processed electroencephalogram-monitored care. The United Kingdom's National Institute for Health and Care Excellence published 2012 guidelines recommending the use of processed electroencephalogram monitoring, especially in "high risk" patients to improve

cognitive outcomes. [16] However, this recommendation is based on limited data, and there is no published meta-analysis that evaluates all trials for either postoperative delirium or postoperative cognitive dysfunction to date.

In the United States, the most recent practice advisory from the American Society for Anesthesiology (ASA) regarding processed electroencephalogram monitoring advocates its use on a "case-by case" basis and does not address the issue of cognition. [17] Therefore, this systematic review and meta-analysis was designed to examine the relationship between processed electroencephalogram monitoring and postoperative delirium/postoperative cognitive dysfunction, specifically to determine if its intraoperative use has utility in minimizing the occurrence of postoperative delirium/postoperative cognitive dysfunction.

Materials and Methods

The primary objective of this review was to assess whether there was a significant association between use of processed electroencephalogram and postoperative delirium/ postoperative cognitive dysfunction. Inclusion criteria were randomized controlled clinical trials that provided original data, patients ≥18 years old, and randomized to intervention-use of a processed electroencephalogram during surgery *vs.* routine-non-use of the monitor, or used processed electroencephalogram to target different output values (high *vs.* low target values). Postoperative delirium or postoperative cognitive dysfunction must have been stated as a primary outcome and measured by a validated scale. The type of anesthetic (such as regional *vs.* general anesthesia) was not an exclusion criterion as we aimed to understand the potential effect of processed electroencephalogram on postoperative cognitive outcomes in *any* patients who requires the care of an anesthesia team.

Identification of studies

An electronic search was completed on Ovid MEDLINE, PubMed, EMBASE, Cochrane Library, and Google search without date restrictions using the following search terms: processed electroencephalogram, bispectral index, postoperative delirium, postoperative cognitive dysfunction. No results in foreign languages were returned; all included papers were published in the English language. 369 results were identified from the electronic databases, which were then pooled and duplicates were removed. One reviewer (KM) screened the remaining 265 abstracts and removed any study not meeting the inclusion criteria, specifically removing all abstracts that were not randomized controlled clinical trials, or did not identify processed electroencephalogram or BIS as an independent variable and postoperative delirium or postoperative cognitive dysfunction as a dependent variable. Two reviewers (KM, JL) independently assessed the remaining 38 full text publications to ensure that they met inclusion criteria. Both reviewers mutually agreed upon the 13 publications selected for inclusion; any disagreements were resolved by discussion (Figure 1).

Quality Assessment

Two reviewers (KM, JL) independently assessed methodological quality of selected studies, discrepancies were resolved by discussion. Studies were given ratings of A (adequate), B

(unclear), or C (inadequate) rating in three different categories: randomization, allocation concealment, and selection bias. The criteria were based off of the Cochrane Risk of Bias scale and are defined in Appendix 1. The reviewers then used three different scales to assess each study: Physiotherapy Evidence Database scale, [18] Jadad scale, [19] and the Cochrane Risk of Bias assessment (Table 1). [20]

Data Extraction

A data extraction form was designed to include: study design (including quality measures outlined above), independent and dependent variables, anesthetic protocol, number of participants, and measured outcomes (including: mean BIS with SD, incidence of postoperative delirium and/or postoperative cognitive dysfunction between study groups with odds ratios (OR), and other publication specific reported outcome measures at specified time points such as Cognitive Failure Questionnaire, Mini Mental State Exam, Trail Making Test, processing speed, working memory, and verbal memory.

Evolution of Objectives

Although postoperative cognitive dysfunction trials were collected and extracted as outlined above, the data were ultimately excluded from the meta-analysis given heterogeneity of outcome measures and instead, and were discussed descriptively. This was the only deviation from the pre-defined objectives.

Data Analysis

Analyses used OR as the effect size measured with 95% confidence intervals (95%CI), significance set at $p<0.05$, with the study as the unit of analysis. A total of 5 trials with postoperative delirium as the primary outcome were included in the meta-analysis to compute the overall pooled-effect estimate examining the relationship between processed electroencephalogram and postoperative delirium.

The overall effect size analyses were computed with the STATA 12.0 (StataCorp; Texas) [21] metan function using the random option to conduct a random-effects method analyses. Additionally, Cochran's Q statistic, which helps detect potential systematic differences in effects sizes between studies, was included in the analyses and evaluated with a chi-squared test and p-value. Significance in the Q test would suggest that heterogeneity exists among the studies in the analytic sample. Furthermore, the I^2 was calculated to represent another index of heterogeneity as the percentage of total variation due to between study differences.

Examination of the pooled estimate and Q statistic suggested that there was no significant heterogeneity detected in the pooled estimate, $\chi^2(4) = 3.7$ ($p=0.46$). This result is further supported based on the $I^2 = 0\%$ in the analysis, suggesting no heterogeneity in the results. Based on the findings, the studies' results only differ by sampling error (chance) and thus a fixed-effects model may be applied to obtain the overall effect size.

Results

Description of studies

The literature search identified 39 potentially relevant articles, including one abstract. [22] The abstract was excluded due to inability to obtain full data set from corresponding author. Twenty-five publications were excluded due to failure to meet inclusion criteria: eight were review articles, [23–31] seven were cohort studies rather than randomized controlled clinical trials,[32–37] six evaluated outcome other than postoperative delirium or postoperative cognitive dysfunction, [34,38–41] two were still ongoing at time of publication,[32,42] one used a different variable than processed electroencephalogram-guided care[43] and one used a data set from a trial already included.[34]

The remaining 13 trials were selected based on inclusion criteria and are included in this review and meta-analysis, three of which reported postoperative delirium and postoperative cognitive dysfunction as outcomes, two reported postoperative delirium only, and eight reported postoperative cognitive dysfunction only (Table 2).

Postoperative Delirium

Five trials were included in the postoperative delirium analysis, with a total of 2,654 subjects, without crossover between standard care *vs.* BIS monitored groups. Study populations ranged from 32 to 1277 subjects. Mean age of patients in each trial ranged from 60 to 82 years. The proportions of women in the reported studies ranged from 37% to 73%. Reported co-morbidities included body mass index, age, sex, education, ASA status, surgery type and duration, presence of depression, preoperative cognitive status, preoperative functional assessment, and preoperative medication use (opioids, benzodiazepines). Chan,[34] Radtke,[44] and Sieber[45] included roughly equal proportions of ASA status patients (I-IV), Jildenstal[46] included only ASA I-II, and Whitlock[47] including a majority of ASA IV patients.

Four of the five trials randomized to processed electroencephalogram-guided anesthesia *vs.* unmonitored care. The trials by Chan *et al.* and Radtke *et al.*[34,44] used a BIS-guided group (with target 40–60 or 50–60) *vs.* a control group of routine care without BIS monitoring: the rate of postoperative delirium was 15.6% in monitored care *vs.* 24.1% in routine care (p=0.01) in the study by Chan et al., and 16.7% *vs.* 21.4% (p=0.036) in the study by Radtke *et al.* Whitlock *et al.*[52] used a BIS-guided group (BIS 40–60) *vs.* a control group of end-tidal anesthetic concentration with goal 0.7–1.3 age-adjusted minimum alveolar concentration and found the rate of postoperative delirium was 18.8% in the BIS group and 28.0% in routine care (p=0.058). Jildenstal et al.[46] used auditory evoked potentials -guided anesthesia with an interventional goal of auditory evoked potentials index of 15–20 *vs.* a control group of unmonitored routine care and found the rate of postoperative delirium was 0% in the interventional group *vs.* 12.5% in the routine care group (p=0.48).

The fifth trial by Sieber *et al.* [48] randomized patients into receiving two different BIS target values - ≥80 (intervention) *vs.* 50 (control); this was the only study in the postoperative delirium analysis that employed spinal anesthesia with propofol sedation rather than using general anesthesia, as well as the only study that designated a numerically lower target goal

instead of routine care without monitoring. The authors state “the sedation criterion in the deep sedation group may be “more representative of actual practice than generally appreciated”; thus, in the meta-analysis the low BIS group data was included with routine care data from the other trials. In this study, Sieber *et al.* [48] found the postoperative delirium rate to be 19% in monitored care with higher targeted BIS values *vs.* 40% in the group with the lower targeted values (p=0.02).

Outcomes were measured by standardized delirium screen in all postoperative delirium trials, with three using Confusion Assessment Method,[50] one using the Confusion Assessment Method for the Intensive Care Unit,[51] and one using psychiatric evaluation with Diagnostic and Statistical Manual IV criteria.[52] The aggregated OR computed between processed electroencephalogram monitoring and postoperative delirium for all five studies using the fixed-effects model was 0.62 (p<0.001; 95% CI, 0.51 to 0.76; I^2=0%; Figure 2). The combined results suggest that processed electroencephalogram-guided anesthesia decreased the odds of developing postoperative delirium by approximately 38%. Because the study by Sieber *et al.* had a slightly different study goal and anesthetic management, we performed additional analysis to determine if the overall results were different if this study was excluded. In the repeated analysis without this study, we found an OR of 0.64 (95%CI, 0.53 to 0.79, p<0.001), which is essentially unchanged from the original result including this study.

Postoperative Cognitive Dysfunction

Eleven randomized controlled clinical trials examining postoperative cognitive dysfunction were identified. Trial sizes ranged from 32 to 1277 subjects. Mean age of included patients in each trial ranged from 37 to 75 years. All trials used general anesthesia.

Three trials[34,44,46] previously discussed are included in this analysis as they measured postoperative cognitive dysfunction in addition to postoperative delirium as an outcome. Wong *et al.*[53] used a BIS-guided group (with target 40–60 or 50–60) *vs.* control of routine care without BIS monitoring. Another trial from Jildenstal *et al.*[54] used anesthesia guided by auditory evoked potentials with a goal auditory evoked potential index (15–20) *vs.* routine care. An *et al.*[55] used a high BIS goal of 55–65 *vs.* a low goal of 30–40 with total intravenous anesthesia. Farag *et al.*[56] used a high BIS goal of 50–60 *vs.* a control low goal 30–40. Ballard *et al.*[57] used a combined intervention of BIS guidance (goal 40–60) with peripheral capillary oxygen saturation monitoring *vs.* routine care. Hou *et al.* [58] used two different BIS goals (55–65 *vs.* 40–50). Two trials[59,60] used a three-way randomization model with intervention groups having BIS goals 50–60 *vs.* 40–50 *vs.* 30–40 (control); Shu *et al.*[61] used general anesthesia while Zhang *et al.* used total intravenous anesthesia.

Postoperative cognitive dysfunction was evaluated with a wide range of neuropsychological test batteries that varied greatly from trial to trial. Time collection of postoperative data points also varied extensively and ranged from 1 day to 1 year after surgery. Given this heterogeneity of outcome measurement, the extracted data were not suitable for meta-analysis. Therefore, a discussion of the studies is summarized descriptively.

Direct comparison of the incidence of postoperative cognitive dysfunction is difficult but across studies, it ranged from 0.01% at one day to 56% at one year in the monitored groups and from 0.07% at one day to 84% at one year in the control groups.

Risk of bias in included studies

As described in *Methods*, the methodological quality of included studies was assessed with respect to randomization, allocation concealment and selection bias. The risk of bias was low for three studies, with unclear assessment for two studies. The full findings are summarized in Table 1.

Discussion

Postoperative Delirium

Of the five randomized controlled clinical trials examined in the postoperative delirium meta-analysis, three [44,45,49] found processed electroencephalogram-guided anesthesia to be associated with significantly decreased risk of postoperative delirium. Whitlock *et al.*[47] found a difference in the rates of postoperative delirium between the BIS-monitored and routine care, but the difference was not statistically significant, and Jildenstal *et al.* [46] found no difference.

Since the trials in the current literature search vary greatly in quality, sample size, and methodology of processed electroencephalogram monitoring, meta-analysis was essential for drawing conclusions that could inform clinical practice. The combined results suggest that use of a processed electroencephalogram may be associated with lower postoperative delirium incidence. However, whether there is a causal mechanism for this decrease is unknown, although hypothesized mechanisms are discussed below.

One of the most common explanations is that the use of processed electroencephalogram monitored care allows the anesthesiologists to reduce the amount of anesthetics administered, therefore resulting in a “lighter” anesthetic depth as shown by the continuous processed electroencephalogram number such as the BIS. This explanation suggests that anesthetic agents by themselves may be deleterious to the brain, therefore reducing the amount administered may result in a lower incidence of postoperative delirium. This hypothesis, however, is unproven by existing studies. In the study by Jildenstal *et al.*[61] which showed that by targeting BIS values of 40–60, doses of hypnotic agents decrease by 11% to 27%[9]. However, this result was contrary to that reported by Radtke *et al.* [44] which showed the amount of anesthetics used between the groups with *vs.* without the use of processed EEG was similar. In fact, in the study by Whitlock *et a*l., [47] the authors reported that the patients with postoperative delirium actually received lower levels of anesthetics. Results from the latter study suggest that factors other than the amount of anesthetics administered may be at play that is affecting the processed electroencephalogram levels, such as patients’ baseline vulnerability.

Prior studies on the use of processed electroencephalogram guided anesthesia focused on factors such as the BIS levels or the amount of burst suppression being predictors of postoperative delirium. [44,62] However, the assumption that the amount of anesthetic given to

older patients directly contributes to acute brain dysfunction and results in subsequent delirium is unproven. Furthermore, previous studies addressing anesthetic depth and cognitive outcomes did not consider preoperative cognitive status as a potential moderator for the effects of anesthetic depth on postoperative cognitive outcomes. Specifically, one of the most important baseline patient related factors contributing to adverse postoperative cognitive outcomes is pre-existing cognitive impairment. Therefore, the depth of anesthesia may simply be a marker for patient's baseline brain vulnerability to the effects of anesthetics. The differentiation between direct effects of anesthetic effects on the brain versus patients' baseline vulnerability is critical to understanding the relationship between delirium and the role of the use of processed electroencephalogram guided anesthesia.

There were several potential limitations to our meta-analysis including the number of trials available, especially with respect to publication bias, as published peer-reviewed trials tend to exclude negative trials. Additionally, two studies received an "unclear" risk of bias score, secondary to incomplete information on the allocation process and handling of exclusions. Both of these studies still received a >3 score on the Jadad score indicating adequacy for meta-analysis.

Another potential limitation is that four of the five studies randomized to processed electroencephalogram-guided care with a higher target *vs.* routine "blinded" care, established on the assumption that unmonitored anesthesia has lower monitor readings, usually a BIS <60. [63] However, Sieber *et al.* [48] had both groups assigned to processed electroencephalogram-guided care (high *vs.* low targets), with the assumption that the "sedation criterion [low BIS target of 50] may be more representative of actual practice". As this represents a variation, repeat meta-analysis excluding this study was performed and did not significantly change the results.

There was also variation in the scales for reporting delirium, although the 3 tools (Confusion Assessment Method, Confusion Assessment Method for the ICU, and Diagnostic and Statistical Manual IV criteria) represent, respectively, highly validated tools and gold-standard evaluation. Additionally, the mean age of patients in the included trials ranged from 60 to 82 years, which could have biased rates of delirium and limited the generalizability of results, especially as there is limited data for delirium incidence in patients >80 years. Lastly, Whitlock *et al.*[47] studied a thoracic and cardiac surgery population, which is known to have higher rates of postoperative delirium,[64] and the findings may not be directly applicable to the noncardiac surgical patient population.

Using the fixed effects model, the assumption is that a common effect size is generalizable only to the population collectively defined by the analyzed studies of older surgical patients. As the studies had analogous interventions and postoperative delirium was assessed using comparable validated scales; statistical criteria were met for the use of a fixed effects model. However, we recognize that the fixed effects model can result in narrower confidence intervals around the effect sizes. All results were verified by a random effects model and were similar.

Lastly, we reported only on the incidence of postoperative cognitive outcomes, rather than the practical sequelae of cognitive impairment such as length of hospital stay or cost-effectiveness.[65] Future research should evaluate the extent and amount of training surrounding the use of processed electroencephalogram, and the costs of equipment and supplies, vis à vis the reduction of adverse postoperative outcomes.

Postoperative Cognitive Dysfunction

An initial aim when designing this meta-analysis was to evaluate the effect of processed electroencephalogram monitoring on postoperative cognitive dysfunction, as it is still unknown if this represents a less severe trajectory of postoperative delirium or if it is a discrete phenomenon with varying etiologies. A recent meta-analysis from Lu *et al.* [66] attempted to delineate this relationship with 4 trials [45,55,56] (including one trial that was excluded from our study because it had an independent variable of dexamethasone administration), [67] and found no significant difference.

Although we selected a moderate number of trials for analysis (n=11), the selected studies ultimately measured postoperative cognitive dysfunction with heterogeneous neurocognitive batteries and different timelines, which made pooled data analysis inappropriate. Additionally, the risk of bias for the postoperative cognitive dysfunction trials was heavily weighted towards high or unclear bias, which a departure from the delirium trials (Table 1). Without a standard definition of postoperative cognitive dysfunction, it is difficult to evaluate the existing publications with meta-analysis.

In two of the trials,[59, 60] the high BIS level groups actually performed significantly worse on outcome measures. Similarly, An *et al.*[55] showed that the rate of postoperative cognitive dysfunction in patients randomized to a lower target was 10% *vs.* 27.5% in the higher target group. Although not a randomized controlled clinical trial, a cohort study by Deiner *et al.* [32] also found that more time spent in at lower levels (BIS <45) and burst suppression was significantly associated with lower rates of postoperative cognitive dysfunction. These results are contradictory to that shown in the delirium studies and clearly need to be confirmed by large randomized trials, including the use of standardized neuropsychological tests and follow up of patients at regular intervals in order to determine the magnitude and duration of postoperative cognitive dysfunction, and its relationship with postoperative delirium. Our review also confirms the need to develop standardized definitions of postoperative cognitive dysfunction.

Summary

Delirium is a geriatric syndrome with many contributing perioperative factors. Use of processed electroencephalogram may be associated with decreased postoperative delirium incidence. However, the mechanism for this association is unknown. Specifically, whether processed encephalographic values are truly modifiable variables in the strategy to prevent or reduce postoperative delirium remains to be tested. Equally unclear is whether the observed processed encephalographic values are simply surrogate markers for the at-risk patients. Finally, the heterogeneous methods in measuring postoperative cognitive dysfunction make it difficult to assess its relationship with processed electroencephalogram.

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Appendix 1. Quality Assessment Criteria

Adequacy of randomization

A. True randomization (i.e. random number table, computer random number generator, *etc.*)

B. Indicating "randomization was done" without providing the details as described in (A).

C. No mention of randomization, allowing choice of cohort, or other non-random method (i.e. medical record number, birth date, *etc.*)

Allocation concealment process

A. Use of central allocation or sequentially numbered opaque, sealed envelopes

B. No mention of allocation concealment approach, or reported an approach not clearly within the bounds of (A) (i.e. mentioning sealed envelopes, but not whether they were opaque or sequentially numbered).

C. Any approach where the research team could possibly predict allocation (i.e. open lists such as a list of random numbers), assignment envelopes without appropriate safeguards (i.e. use of unsealed, transparent or not sequentially numbered envelopes).

Selection bias with respect to subject attrition

A. No missing outcome data or loss to follow-up <10%, reasons for missing outcome data mentioned, missing data balanced between cohorts, intention-to-treat analysis

B. Insufficient reporting of attrition and exclusions to permit adequate judgment

C. Loss to follow-up >10%, reason for missing outcome data likely to be related to true outcome, disparity in missing data between cohort groups, 'as-treated' analysis

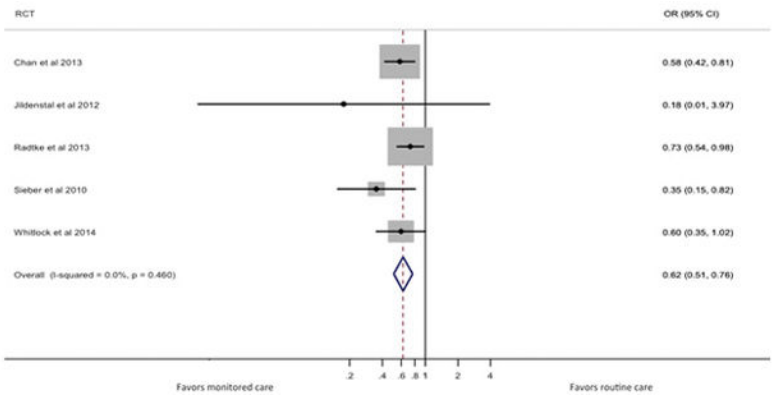

Figure 1. Flow diagram indicating study selection process

RCT = randomized controlled trail; POD = postoperative delirium; POCD = postoperative cognitive dysfunctiion.

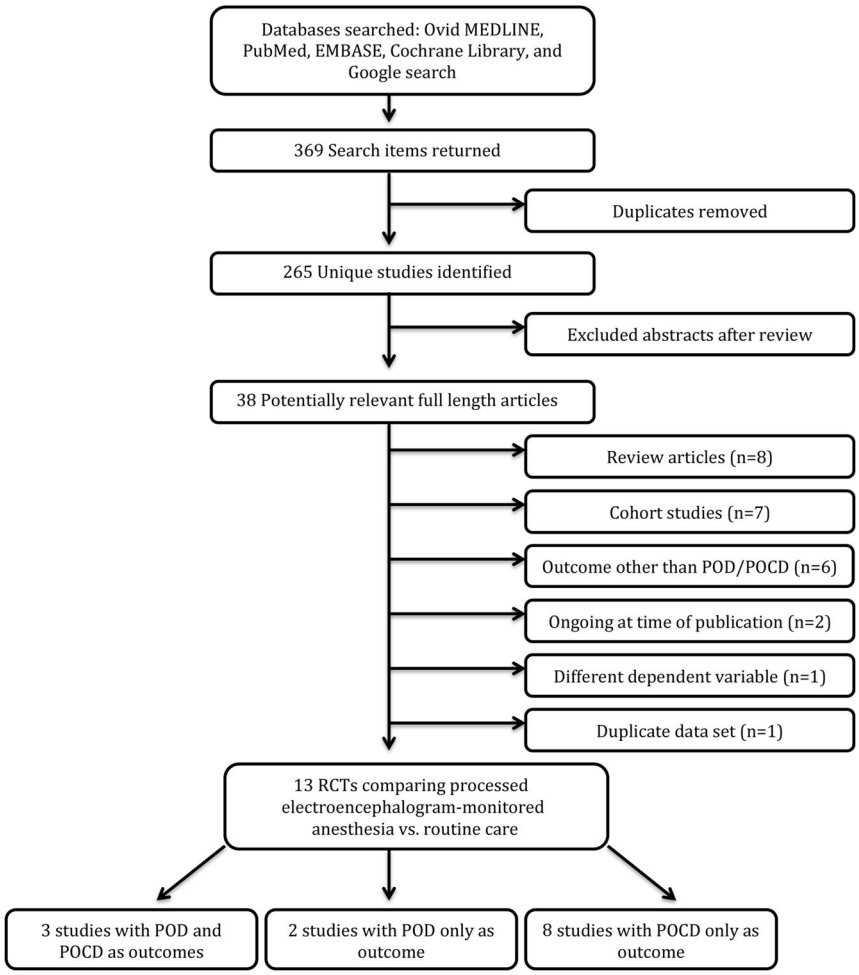

Figure 2.

Forest plot of odds ratios (OR, solid dots) for postoperative delirium in the trials of processed electroencephalogram-guided (high target) vs. routine (low target) anesthesia. The gray squares are shown in size proportional to weight assigned in meta-analysis. The aggregated odds ratio is shown as the vertical dotted line. Associated 95% confidence intervals are indicated by the solid bars and lateral tips of the diamond

Table 1

Methodological Quality Assessment.

Study ID	Randomization	Allocation	Selection bias	>50 subjects per arm	PEDro	Jadad	Cochrane Risk of Bias
Studies examining POD and POCD							
Chan et al. (2013)[48]	A- adequate	A- adequate	A-adequate	yes	10	4	Low
Jildenstal et al. (2012)[51]	A- adequate	A- adequate	A- adequate	no	9	4	Low
Radtke et al. (2013)[49]	A- adequate	B- unclear	A-adequate	yes	10	3	Unclear
POD only							
Sieber et al. (2010)[50]	A- adequate	A- adequate	A- adequate	yes	10	4	Low
Whitlock et al. (2014)[52]	A- adequate	A- adequate	B- unclear	yes	9	4	Unclear
POCD only							
An et al. (2011)[61]	B- unclear	B- unclear	C- inadequate	no	9	2	Unclear
Ballard et al. (2012)[62]	A- adequate	B- unclear	C-inadequate	no	9	3	High
Farag et al. (2006)[58]	B- unclear	B- unclear	C- inadequate	no	7	2	High
Hou et al. (2018)[61]	A- adequate	B- unclear	A- adequate	no	7	3	Unclear
Jildenstal et al. (2011)[60]	A- adequate	A- adequate	B- unclear	yes	9	4	Unclear
Shu et al. (2015)[56]	A- adequate	B- unclear	A- adequate	yes	9	4	Unclear
Wong et al. (2002)[59]	A- adequate	B- unclear	C- inadequate	no	9	4	Unclear
Zhang et al. (2016)[57]	A- adequate	A- adequate	A- adequate	yes	10	5	Low

POD= postoperative delirium; POCD= postoperative cognitive dysfunction; PEDro= Physiotherapy Evidence Database

Table 2

Characteristics of Included Studies.

Authors	Study population	Variables	Outcomes	Anesthetic protocol
Studies examining POD and POCD				
Chan et al. (2013)[48]	921 patients >60 years undergoing major noncardiac surgery, excluded those with suspected dementia or MMSE <23	**Intervention:** BIS-guided (40–60) **Control:** Routine care	**POD** as assessed by CAM; **POCD** assessed by neuropsychological battery of tests was administered preoperatively, 1 week, and 3 months postoperatively.	GA
Jildenstal et al. (2012)[51]	32 patients 40 to 94 years, scheduled for Ear, Nose, and Throat (ENT) surgery	**Intervention:** AAI-guided (15–25= goal) **Control:** Routine care	**POD** as assessed by CAM on postoperative day 1. **POCD** as assessed by MMSE on postoperative day 1, CFQ at 1 month postoperatively.	GA
Radtke et al. (2013)[49]	1277 general surgery patients >60 years, excluded patients with MMSE <24 or pre-existing neurological condition	**Intervention:** BIS-guided (40–60) **Control:** Routine care	**POD** as assessed by DSM-IV criteria postoperative days 1–7, twice a day. **POCD** as assed by neuropsychological test battery (Motor Screening Test, two tests of visual memory, attention, visual verbal learning test, Stroop Color Word interference test) was evaluated at baseline, 1 week, and 3 months	GA
POD only				
Sieber et al. (2010)[50]	114 patients ≥65 years without preoperative delirium or severe dementia who underwent hip fracture repair	**Intervention:** Light anesthetic depth (BIS, ≥80). **Control:** Deep anesthetic depth (BIS, approximately 50)	**POD** as assessed by CAM	Spinal anesthesia with propofol sedation
Whitlock et al. (2014)[52]	310 patients >18 years after cardiac or thoracic surgery in the ICU	**Intervention:** BIS-guided (alerts for BIS>60 or BIS<40) **Control:** ETAC-guided (alerts for <0.7 or >1.3 age-adjusted MAC)	**POD** as assessed by CAM-ICU performed twice daily until postoperative day 10 or ICU discharge, whichever occurred first.	GA
POCD only				
An et al. (2011)[61]	96 patients 28 to 67 years with facial spasm undergoing microvascular decompression	**Intervention:** Light anesthetic depth (BIS 55–65) **Control:** Deep anesthetic depth (BIS 30–40)	**POCD** as assessed by a battery of 9 neuropsychological tests (positive for POCD required 2+ deficits of >1 SD between preoperatively and 5 days postoperatively).	TIVA
Ballard et al. (2012)[62]	72 patients >60 years undergoing elective orthopedic or abdominal surgery	**Intervention**: Combined BIS-guided (40–60) *and* spO_2 monitoring **Control**: Routine care	**POCD** as assessed by reaction time, trail making, and MMSE at 1 week, 12 weeks, and 52 weeks.	GA
Farag et al. (2006)[58]	74 patients >50 years undergoing spine, abdominal, and pelvic surgery	**Intervention:** Light anesthetic depth (BIS target of 50–60 during surgery and 55–70 during wound closure.)	**POCD** as assessed by a battery consisting of processing speed index, working memory index, and verbal memory index 4–6 weeks postoperatively.	GA

Authors	Study population	Variables	Outcomes	Anesthetic protocol
		Control: Deep anesthetic depth (BIS target of 30–40 during surgery and 50–60 during closure.)		
Jildenstal et al. (2011)[60]	450 patients 18 to 92 years scheduled for ophthalmic surgery	**Intervention:** AAI between 15 and 25 **Control:** Routine care	**POCD** as assessed by MMSE, CFQ, and Activities of Daily Living at 1 day, 1 week, and 1 month postoperatively.	GA
Shu et al. (2015)[56]	192 patients 20 to 60 years undergoing gynecologic laparoscopic operations	**Intervention:** BIS 40–50 *or* BIS 50–60 (three-way randomization) **Control:** BIS 30–40	**POCD** as assessed by MMSE and TMT on postoperative day 1.	GA
Wong et al. (2002)[59]	68 patients >60 years undergoing elective orthopedic surgery	**Intervention:** BIS goal 50–60 **Control:** Routine care	**POCD** as assessed by MMSE, Trieger Dot Test, and Digit Symbol Substitution Test at 30 min intervals after discontinuation of anesthesia to 120 minutes, then at 24, 48, and 72 hours	GA
Zhang et al. (2016)[57]	150 patients 21 to 57 years undergoing gynecological laparoscopic operation	**Intervention:** BIS 40–50 *or* BIS 50–60 (three-way randomization) **Control:** BIS 30–40	**POCD** assessed by MMSE and TMT on postoperative day 1.	TIVA

AAI= auditory evoked potential (AEP) index; BIS= bispectral index; CAM= Confusion Assessment Method; CAM-ICU= Confusion Assessment Method for the Intensive Care Unit; CFQ= Cognitive Failures Questionnaire; DSM-IV= Diagnostic and Statistical Manual, 4th ed.; ETAC= end-tidal anesthetic concentration; GA= General Anesthesia; MMSE= Mini Mental State Exam; POCD= postoperative cognitive dysfunction; POD= postoperative delirium; spO_2= peripheral capillary oxygen saturation; TIVA= total intravenous anesthesia; TMT= Trail Making Test