Effects of Electroencephalogram Guided Anesthesia on Postoperative Delirium: A Systematic Review and Meta-analysis

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Lin Ding
Sichuan University West China Hospital

DongXu Chen
Sichuan University West China Hospital

Qian Li
Sichuan University West China Hospital

✉ sculiqian@foxmail.com Corresponding Author
ORCID: https://orcid.org/0000-0003-3301-4284

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Abstract

Background: Postoperative delirium is a common complication characterized by confusion, inattentiveness and other mental symptoms. It is still unclear whether the use of electroencephalogram (EEG) monitoring during surgery can decrease the incidence of postoperative delirium. The purpose of this study was to evaluate the effectiveness of EEG guided anesthesia on postoperative delirium (POD) based on randomized controlled trials (RCTs).

Methods: The electronic databases of Ovid MEDLINE, PubMed, EMBASE, Cochrane Library database, CNKI and other local databases were systematically searched for RCTs from their inception until October 2019. The odds ratios (ORs) and the mean differences (MDs) with a 95% confidence intervals (CIs) were calculated to evaluate the correlation between EEG and itemized categories and continuous variable, respectively.

Results: Seven RCTs with 3859 patients were included in the final analysis. The summary OR indicated that patients receiving EEG monitoring had a lower incidence rate of postoperative delirium (OR: 0.65; 95% CI: 0.46-0.92; P = 0.01). In addition, no significant difference was found between the EEG monitoring group and the routine care group with respects to the length of hospitalization (MD: -0.59; 95% CI: -1.26 to 0.07; P=0.08).

Conclusions: The findings of this study indicated that intraoperative use of electroencephalogram monitoring could decrease the risk of postoperative delirium. But for high risk patients, we should take a multi-component strategy to prevent delirium. Further large-scale, randomized controlled trials should be conducted to verify the treatment effect of intraoperative use of electroencephalogram monitoring on patients.

Introduction

Delirium is an acute disorder of mental dysfunction, characterized by confusion, inattentiveness, disorientation, agitation, and in some cases, excessive autonomic nervous system activity [1]. Postoperative delirium (POD) is a common complication after surgery, with a general incidence rate ranging from 10%-50%. In high-risk patients, the incidence rate of POD can reach as high as 50-70% [2-4]. POD is associated with several poor prognosis factors, including higher mortality, long-term
cognitive decline, dementia, re-admission and prolonged length of hospitalization. It also increases the financial burdens to the public, reaching up to $16 billion for US health care cost every year [4-10].

Various risk factors have been reported to be associated with postoperative delirium, such as the use of drugs, inflammation, and metabolic abnormalities [11]. Notably, some studies revealed that excessively deep depth of anesthesia increased the risk of postoperative delirium [12-14].

Electroencephalography (EEG) is commonly used for monitoring the depth of anesthesia [15]. Burst suppression, an EEG pattern featuring flat periods of high-voltage, slow wave electrical activity with inter-burst refractory periods, often suggests excessively deep depth of anesthesia [16, 17]. Although it remains controversial whether the burst suppression pattern of EEG during surgery correlates with the risk of postoperative delirium, Fritz et. al. reported that the burst suppression characteristic of EEG could serve as an independent risk factor for postoperative delirium [18]. Previous meta-analysis indicated that the use of EEG monitoring during surgery correlated with a reduced risk of postoperative delirium [19]. However, the recently published result of a randomized controlled trial (RCT) addressing the same question, which was conducted by Widles et. al and enrolled 1213 patients, was not consistent with the conclusion [20].

To better understand the effects of EEG monitoring on POD and to provide clearer guidance to clinicians, we conducted this systematic review to investigate the relationship between EEG monitoring during surgery and the adverse clinical outcomes.

**Materials And Methods**

This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) guidelines [21]. This systematic review and meta-analysis had been registered in the international prospective register of systematic reviews (CRD42019130512 https://www.crd.york.ac.uk/prospero/).

**Search Strategy**

Two investigators (DL and DXC) performed a systematic search in the databases of Ovid MEDLINE,
PubMed, EMBASE, Cochrane Library database, CNKI and other databases updated to October 2019. The full search terms for PubMed was: ((((((Electroencephalography [MeSH Terms]) OR Electroencephalography [Title/Abstract]) OR electroencephalogram [Title/Abstract]) OR bispectral index[Title/Abstract]) OR BIS [Title/Abstract]) OR Auditory Evoked Potential [Title/Abstract]) OR AEP [Title/Abstract]) OR depth of anesthesia [Title/Abstract])) AND ((delirium [MeSH Terms]) OR deliri* [Title/Abstract]). The search terms were modified for each database. Any conflicts about search result between the two investigators (DL and DXC) were resolved by discussion and the consensus was reached.

**Eligibility Criteria**

Prior to the systematic review and meta-analysis, the inclusion criteria were predetermined by all authors. Inclusion criteria are as the following: (1) the study was randomized controlled trial (RCT), regardless of publication language and status; (2) patients were adults aged 18 years or older who underwent general anesthesia for surgery; (3) the outcomes of using processed EEG and routine care were compared; (4) the occurrence of POD assessed by validated scale was reported in the study. The exclusion criteria were: (1) non-randomized studies; (2) non full-text studies; (3) ongoing studies; (4) the outcome data could not be extracted and used for analysis.

**Data Collection and Quality Assessment**

The data was extracted by two investigators (DL and DXC) independently using a standardized form based on the PICO approach. This form includes the first author, year of publication, study design, sample size, outcome variables and assessment scale, summative results and conclusion. The methodological quality of the included studies was assessed using the Cochrane risk of bias scale, which contains seven specified domains [22]. Risk of bias were classified as high, low or unclear for each item. The quality assessment was conducted by two investigators independently, and any conflicts was resolved by a third investigator (QL) referring to the original article.

**Statistical Analysis**

Data analyses were performed using Review Manager (version 5.3). The inspection level for the pooled data were 2-sided, and P < 0.05 was regarded as statistically significant. The odds ratio (OR)
and mean difference (MD) with 95% confidence interval (CI) were employed for analyzing the categories and continuous data. The standard difference was calculated with the formula: (Maximum-Minimum)/4 \[23\]. Heterogeneity across studies was assessed with chi-square test and I² test, and I² >50% or P < 0.10 was considered as significantly heterogenous. The random-effect model was adopted if the heterogeneity existed among the studies, whereas the fixed-effect model was applied if no significant heterogeneity was detected \[24-26\]. Sensitivity analysis was conducted to assess the impact of single study to the overall analysis \[27\]. Publication bias was assessed using the Egger and Begg test \[28, 29\].

Results

Literature Search

The initial searches in PubMed, Ovid, EMBASE, Cochrane library, CNKI and Chinese local databases identified 770 reports. Duplicates removal reduced the number of reports to 682. Then, 662 studies were excluded after reviewing the title and abstracts. The full text of the remaining 20 studies were retrieved for evaluations, in which 13 studies were further excluded due to one or more of the following reasons: not RCT (n=2) \[30,31\]; review (n=3) \[32-34\]; non-general anesthesia patients (n=2) \[12,13\]; the control group used end-tidal anesthetic concentration (ETAC) as a guide for anesthesia depth rather than routine care (n=1) \[35\]; no full-text available (n=1) \[36\], or ongoing studies (n=4). Reviewing the reference lists of retrieved studies did not identify any new eligible study. Finally, seven RCTs were included in this review \[20, 37-42\]. A flow diagram illustrating the literature search and trials screening process was shown in Figure 1.

Characteristics of Included Studies

As listed in Table 1, seven RCTs including a total number of 3859 patients were enrolled in this meta-analysis. Six out of the seven studies used bispectral index (BIS), and the last one, conducted by Jidenstal et. al \[37\], used auditory evoked potential (AEP) as the guide for anesthesia depth. One trial included patients who underwent cardiac surgery \[20\], whereas the other six studies were conducted in patients who underwent major non-cardiac surgery, including abdominal surgery, ENT surgery and
hip fracture repair surgeries. The assessment result of risk of bias was shown in Figure 2 (figure2A: risk of bias summary: review authors’ judgements of each risk of bias; B: risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all). As shown in the figure 2, the study conducted by Li et al. was at high risk of bias due to the absence of the methods of allocation and blinding [42]. Two studies were at unclear risk of bias due to the unclear blinding of outcome assessments (detection bias) or unclear blinding of participants and study personnel (performance bias) [39, 41]. And the remaining 4 studies were at low risk of bias.

**Postoperative Delirium (POD)**

After pooling the data from all the included studies (n=3859, EEG monitoring=1924, routine care=1935), we noticed that patients in EEG-guided anesthesia group had a reduced risk of postoperative delirium as compared to the patients in the group of routine care (OR: 0.65; 95% CI: 0.46-0.92; P = 0.01); (Figure 3), but the heterogeneity among included studies was detected (P=0.002, $I^2=71\%$). Sensitivity analysis result indicated that the study conducted by Wildes et al. [20] (n=1213, EEG monitoring =604, routine care=609) contributed to the heterogeneity, but the result was not changed by excluding this specific trial (OR: 0.60; 95% CI: 0.50-0.73; P < 0.00001) from our study. Base on Egger (P=0.283) and Begg (P=0.452) tests, no significant publication bias in terms of postoperative delirium was found.

**Length of Patient Hospitalization**

Data from 4 trials including 3450 patients were analyzed regarding the length of hospitalization between the EEG monitoring group and the routine care group [20,38-39,41]. Three of the four studies (n=3270, EEG monitoring =1629, routine care=1641) didn’t demonstrate significant difference between the EEG guided anesthesia group and routine care group [22, 38, 39] with respect to the length of hospitalization. Qiang et al. (n=180, EEG monitoring=90, routine care=90) reported a significantly longer hospital-stay for patients in the routine care group compared to that of the patients in the EEG monitoring group [41]. The analysis result of all the patients in the four studies didn’t support the conclusion that the use of intraoperative EEG monitoring could reduce the length of hospitalization
(MD: -0.59; 95%CI: -1.26 to 0.07; P=0.08). Detailed result was shown in Figure 4. Furthermore, significant heterogeneity was observed in the studied trials (P=0.03, $i^2=65\%$).

**Mortality**

Two studies (n=2368, EEG monitoring=1179, routine care=1189) investigated the postoperative mortality. Radtke *et al.* (n=1155, EEG monitoring=575, routine care=580) reported that the 3-month mortality was not significantly different between the EEG-guided anesthesia group and the routine care group. However, Wildes and his colleagues (n=1213, EEG monitoring =604, routine care=609) revealed that the 30 days postoperative mortality rate was lower in patients receiving intraoperative EEG guided anesthesia (p=0.004) than that of the patients in the routine care group. The meta-analysis was not conducted for mortality due to the limited data and the high heterogeneity of the trials.

**Discussion**

In the present systematic review and meta-analysis, seven RCTs with 3859 patients, including 1924 patients who received EEG-guided anesthesia and 1935 patients who received routine care were enrolled. We found the incidence of postoperative delirium was significantly reduced in the EEG-guided group compared to the routine care group. However, there was no difference regarding the length of hospitalization between the two groups. No analysis was performed on mortality rate due to limited data and the high heterogeneity of reenrolled studies.

Prior to our study, Kristen *et al.* and Punjasawadwong *et al.* have performed two meta-analyses independently, including 3 RCTs (n = 2197) and 5 RCTs (n = 2654) respectively, to evaluate the impact of EEG monitoring on POD and postoperative cognitive dysfunction (POCD). Both meta-analyses reported that the EEG-guided anesthesia could reduce the incidence of POD. But the authors also pointed out that the quality of the research evidence was moderate, and future studies should be required to clarify whether the appropriate EEG during surgery can reduce the occurrence of POD. It is worth noting that one recently added large-sample RCT (n = 1213) conducted by Wildes and his colleagues proposed that EEG-guided anesthesia could not reduce the incidence of POD, which was
inconsistent with previous large-sample studies \cite{38-39}. In 2013, Chan et. al performed an RCT with 902 patients and revealed that the incidence rate of POD was lower in patients receiving EEG-guided anesthesia than that in patients receiving routine care \cite{38}. In addition, Radtke and his colleagues analyzed information from 1155 patients and concluded that EEG monitoring correlated with a significant reduction of POD incidence \cite{39}. These discrepant findings may attribute to the methodological differences and the heterogeneity of the studied population among those studies.

Compared to the studies by Chan and Radtke et. al\cite{38, 39}, the study conducted by Wildes et. al\cite{20} included patients with more severe conditions. More than 30% of the patients in Wildes’ study had ASA ≥ 3 or had a history of falls or planned cardiothoracic surgery, all of which are risk factors for POD \cite{54-56}. For these high-risk patients, it is recommended in several clinical practice guidelines that a multi-component strategy is needed to prevent delirium \cite{43, 44}, indicating that a single approach of monitoring has limited effect on these high-risk patients to prevent POD occurrence. An ongoing study in patients undergoing cardiac surgery may provide further evidence to verify the conclusion \cite{45}.

However, our meta-analysis suggested that the EEG monitoring significantly correlates with a lower risk of POD.

However, the underlying mechanisms of the POD prevention by EEG monitoring remains unclear. One hypothesis is that the use of EEG monitoring makes it possible to avoid too deep anesthesia, therefore to specifically reduce the incidence and cumulative duration of intraoperative burst suppression. Previous studies have shown that burst suppression is an independent risk factor of postoperative delirium \cite{18, 46}, and Hesse et al. have demonstrated that every incidence of burst suppression during the anesthesia maintenance is associated with a 75% increase in odds of postoperative delirium \cite{31}. Furthermore, high incidence or longer duration of burst suppression are significantly associated with the incidence of postoperative delirium \cite{46-48}. In addition, the use of EEG monitoring also reduce the dosage of general anesthetics, such as volatile agents and propofol \cite{49, 50}. Previous studies have reported that excessively exposure to potent volatile agents might
increase the incidence of POD\textsuperscript{[51]}. Particularly, most of these studies were performed in geriatric patients whose aging brains are more sensitive to anesthetic agents, therefore are more likely to experience the burst suppression and POD\textsuperscript{[52-53]}.

Our meta-analysis results indicated that use of EEG monitoring can reduce the incidence of postoperative delirium, while no effect of EEG on the length of hospitalization was found. In the present study, 4 RCTs including 3450 patients were evaluated with respects to the effect of EEG on the length of hospital stay, only one study with a small sample size of 180 patients indicated that EEG-guided anesthesia could reduce the length of hospitalization. However, hospitalization length is affected by many factors in addition to the postoperative delirium, and the length of hospital stay is not the primary evaluated outcome in the analyzed reports in our study. Therefore, it is difficult to rule out the impacts of other confounding factors and further investigation is needed to clarify the correlation.

In addition, we intended to analyze the mortality between the two groups. However, only two of seven included studies reported the mortality rate. Wildes et al.\textsuperscript{[20]} revealed a significantly higher odd of 30-day mortality in patients without using EEG monitor, as compared to the routine care group. While in Readtke’s report\textsuperscript{[39]}, it was shown that the use of processed EEG had no influence on the 3-month mortality rate. Furthermore, a previous meta-analysis indicated that deep anesthesia had no effect on long-term mortality\textsuperscript{[57]}, which is consistent with a recently published multicenter RCT\textsuperscript{[58]}.

Several limitations of this meta-analysis should be acknowledged: (1) smaller number of included trials and the deviations in the results due to the absence of adjustment variables such as age, gender and the type of surgery; (2) the scales and methods of delirium evaluation varies among the included studies; (3) this study is based on the published articles, the publication bias is inevitable; (4) the analysis of this study is based on data at study-level, whereas the original data from individual patients was not available.

Conclusions
In conclusion, the findings of this study indicated that the use of EEG monitoring correlated with a
lower risk of postoperative delirium. Therefore, we recommend using EEG monitoring during surgery to reduce the risk of postoperative delirium. But for high risk patients, we should combine multiple interventions to optimize perioperative anesthesia for the prevention from postoperative delirium. Further large-scale RCTs should be conducted to verify the correlation between the use of electroencephalogram monitoring and postoperative delirium based on original data directly from patients.

Abbreviations
EEG: Electroencephalogram; POD: Postoperative delirium; BIS: bispectral index; AEP: auditory evoked potential; POCD: postoperative cognitive dysfunction; ETAC: end-tidal anesthetic concentration; ENT: ear, nose, and throat; CI: Confidence interval; OR: Odds ratio; RCTs: Randomized controlled trials; MD: mean difference.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
DL, DXC, and QL designed the study, DL and DXC conducted database searches and extracted study data, DL performed the data analysis, and was a major contributor in writing the manuscript, QL provided critical review
and modification of the manuscript. The authors read and approved the final manuscript.

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Table
Due to technical limitations, Table 1 is only available for download from the Supplementary Files section.

Figures
Figure 1

A flow diagram illustrating the literature search and trials screening process.
| Year | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|------|--------------------------------------------|----------------------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------------------|---------------------------------------|----------|
| 2019 | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Red](red) ![Red](red) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) |
| 2019 | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Red](red) ![Red](red) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) |
| 2018 | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Red](red) ![Red](red) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) |
| 2017 | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Red](red) ![Red](red) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) | ![Green](green) ![Green](green) ![Green](green) ![Green](green) |

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Figure 2

2A: risk of bias summary: review authors’ judgements of each risk of bias; B: risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all

| Study or Subgroup | Electromyograph-guided | Routine-Care | Odds Ratio | M.H. Random, 95% CI |
|-------------------|------------------------|--------------|------------|---------------------|
| Chan 2013         | 70                     | 450          | 109        | 452                 | 0.58 (0.42, 0.91) |
| Jidrenstal 2012   | 0                      | 16           | 2          | 16                  | 1.28 (0.35, 2.31) |
| Li 2014           | 20                     | 147          | 41         | 148                 | 0.41 (0.23, 0.74) |
| Gold 2016         | 16                     | 30           | 30         | 12.5%               | 0.48 (0.24, 0.95) |
| Reifke 2013       | 95                     | 575          | 124        | 590                 | 0.73 (0.54, 0.98) |
| Wildes 2019       | 157                    | 694          | 140        | 699                 | 1.18 (0.91, 1.53) |
| Zhou 2018         | 7                      | 42           | 11         | 40                  | 0.53 (0.24, 1.13) |
| Total (95% CI)    |                        | 1924         | 1935       | 100.0%              | 0.65 (0.46, 0.92) |

Total events: 3855

Heterogeneity: Tau² = 0.12; Chi² = 20.35, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 2.45 (P = 0.01)

Figure 3

After pooling the data from all the included studies (n=3859, EEG monitoring=1924, routine care=1935), we noticed that patients in EEG-guided anesthesia group had a reduced risk of postoperative delirium as compared to the patients in the group of routine care (OR: 0.65; 95% CI: 0.46-0.92; P = 0.01); but the heterogeneity among included studies was detected (P=0.002, I²=71%).
Figure 4

Detailed result of all the patients in the four studies

Supplementary Files

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PRISMA 2009 checklist (1).doc
Table 1 Characteristics of included studies.doc