Effects of anesthetic depth on postoperative cognitive dysfunction (POCD) in non-cardiac surgical patients: a meta-analysis

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Abstract: Objective: The current study aimed to summarize related published articles concerning the depth of anesthesia and postoperative cognitive dysfunction (POCD) in non-cardiac surgical patients. Moreover, this study aimed to investigate the effects of the depth of anesthesia on short- or long-term POCD. Methods: Medline, Embase, Ovid, Cochrane Library, Google Scholar, CNKI, and Wan-fang databases were searched. Researchers focused on the effects of the depth of anesthesia on POCD and on postoperative S100-β protein levels. Results: A total of 2,625 patients from 20 randomized controlled trials (RCTs) were enrolled. The current meta-analysis shows that deep anesthesia significantly decreased incidence of POCD, compared with light anesthesia, on day 1 [OR, 0.31; 95% CI (0.24, 0.40), P < 0.00001], from 3 to 5 days [OR, 0.35; 95% CI (0.24, 0.52), P < 0.00001], day 7 [OR, 0.45; 95% CI (0.27, 0.74), P=0.002], and from 1 to 3 months [OR, 0.66; 95% CI (0.45,0.99), P=0.04] after surgery. Serum S100-β protein levels in patients that received deep anesthesia were much lower than those in patients receiving light anesthesia [MD, -270.29; 95% CI (-295.81, -244.77), P < 0.00001] on postoperative day 1. Conclusion: Deep anesthesia can significantly reduce incidence rates of short- or long-term POCD. Serum S100-β protein levels on postoperative day 1 could be reduced with deep anesthesia.

Keywords: Anesthetic depth, POCD, S100-β protein, non-cardiac surgery, meta-analysis

Introduction

Postoperative cognitive dysfunction (POCD) is a common complication in non-cardiac surgical patients [1-3]. POCD can remarkably increase the cost of care and hospitalization expenses, while decreasing patient quality of life [4, 5]. The relationship between anesthetic depth and POCD has attracted much attention. Extensive research in this area has been conducted. However, controversies remain concerning the results of these studies. Some studies have shown that deep anesthesia could reduce incidence of POCD [6, 7], while others have found that anesthetic depth had no effects on POCD [8, 9]. Devices and techniques for monitoring anesthetic depth have developed rapidly in recent years. Monitoring parameters mainly include the bi-spectral index (BIS), auditory evoked potential (AEP), auditory evoked potential index (AAI), Narcotrend index (NTI), Narcotrend scale (NTS), and cerebral state index (CSI). Therefore, the current meta-analysis concerning the depth of anesthesia and POCD in non-cardiac surgical patients was conducted, aiming to determine the effects of anesthetic depth on POCD and levels of serum S100-β protein, an early and sensitive marker of brain insult [10, 11].

Materials and methods

Study identification

The current meta-analysis aimed to identify all clinical randomized controlled trials (RCTs) concerning the effects of the depth of anesthesia on short- or long-term POCD, as well as postoperative S100-β protein levels, in non-cardiac surgical patients.

Data sources and search strategy

This meta-analysis was conducted in accordance with methods recommended by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) and the
Cochrane Handbook for systematic reviews of interventions [12]. Based on keywords or MeSH terms, including “depth of anesthesia”, “anesthetic depth”, “consciousness monitors”, “bispectral index”, “BIS”, “auditory evoked potential”, “AEP”, “auditory evoked potential index”, “AAI”, “cerebral state index”, “CSI”, “Narcotrend”, “NTI”, “NTS”, “postoperative cognitive dysfunction”, “POCD”, “S100-β”, “S100b”, and “S100beta”, an electronic search for relevant articles was conducted in Medline (-present), Embase (-present), Ovid (-present), the Cochrane Library (-present), Google Scholar (-present), China National Knowledge Infrastructure (CNKI, -present), and Wan-fang (-present) databases without language restrictions.

**Literature screening**

After a thorough literature search, two investigators (Ran An and Qianyun Pang), independently, reviewed the titles and abstracts of all identified studies. They excluded those that were obviously irrelevant or duplicates. Full articles of the remaining studies were then reviewed using a structured form, determining their eligibility and extracting data. Disagreements were resolved by discussion with all authors, if necessary. The authors were contacted for clarification and further information when necessary.

**Inclusion and exclusion criteria**

Inclusion criteria: (i) Trials with a clear boundary of anesthetic depth; (ii) Trials involving elective non-cardiac surgery under general anesthesia; (iii) Trials with patients older than 18 years old; (iv) Randomized controlled trials (RCTs); and (iv) Trials that mentioned incidence of POCD or serum S100-β protein levels. Exclusion criteria: (i) Patients with serious diseases (severe heart disease, kidney failure, respiratory failure, severe systemic infections); (ii) Patients with neurological or mental disorders/or those that took psychiatric drugs preoperatively; (iii) Patients with Alzheimer’s disease or severe cognitive dysfunction; (iv) Patients that were unable to communicate or had preoperative MMSE scores < 17; (v) Patients with history of brain surgery or cerebral trauma; and (vi) Patients with a history of alcohol abuse or drug addiction.

**Quality assessment**

Risk of bias was checked by appraising various parameters, including “adequate sequence generation” “allocation concealment”, “blinding”, “incomplete outcome data addressed”, “free of selective reporting”, and “free of other bias”. As recommended by the Cochrane Collaboration Publication, bias was evaluated using Egger’s test with Stata 12.0 software (College station, TX, USA). \( P > 0.05 \) indicates no statistically significant publication bias.

**Data extraction**

Data regarding the number of patients, patient age, basic information of the study, research title, first author, and publication times, research design types, key elements of evaluation, methods of POCD assessment, types of surgery, incidence of POCD, and S100-β protein levels were extracted from included articles.

**Statistical analysis**

The current meta-analysis was performed using Review Manager Version 5.3 for Windows (the Cochrane Collaboration, Oxford, UK).
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Calculations of effect size for continuous data are expressed as the mean difference (MD). Dichotomous data are expressed as odds ratios (OR) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using $I^2$ statistics. Heterogeneity was significant when $I^2 \geq 50\%$ or $P < 0.01$. Thus, a random-effects model was used. Planned subgroup analyses were conducted, identifying potential sources of heterogeneity. If necessary, a fix-effects model was used when $I^2 \leq 50\%$ or $P \geq 0.01$.

Results

Literature search findings

A total of 352 relevant articles were identified through keywords and MeSH terms. After screening and conducting a detailed selection process, 20 RCTs remained with 2,625 patients [13-32]. Details of the screening process are presented in Figure 1. Risk of bias is summarized in Figure 2. For anesthetic depth monitoring in these 20 RCTs, BIS was used in 11 trials, NTI was used in 7 trials, AAI was used in 1 trial, and CSI was used in 1 trial. To diagnose POCD, the Mini-mental State Examination (MMSE) was used in 11 RCTs, the value Z was used in 3 RCTs, and standard deviation (SD) was used in 4 RCTs. There were no descriptions of the methods for POCD diagnosis in the remaining 2 RCTs (Table 1).

Results of the meta-analysis

Effects of anesthetic depth on short-term POCD: A total of 13 RCTs with 1,287 patients [15-27] analyzed the impact of anesthetic depth on POCD on day 1 after surgery. $I^2=0$ and a fixed-effects model was used. There were 7 RCTs (n=703) that reported the effects of anesthetic depth on POCD from 3 to 5 days after surgery [13, 17, 19-21, 24, 27]. $I^2=0$ and a fixed-effects model was used. A total of 9 RCTs (n=1617) reported the effects of anesthetic depth on POCD on day 7 after surgery [15-17, 19, 20, 28-31]. $I^2=53\%$ and a random-effects model was used. Results showed much lower incidence rates of POCD in the deep anesthesia group, compared to the light anesthesia group, on day 1 [OR, 0.31; 95% CI (0.24-0.40), $P < 0.00001$], from 3 to 5 days [OR, 0.35; 95% CI (0.24-0.52), $P < 0.00001$], and on day 7 [OR, 0.27; 95% CI (0.27-0.74), $P=0.002$] after surgery (Figure 3). There was no significant publication bias, according to Egger’s testing ($P=0.357$, $P=0.284$, $P=0.264$).

Subgroups were created to analyze the effects of anesthetic depth on POCD on day 7 after surgery. BIS values were used in 5 RCTs (n=1279) [14, 17, 19, 20, 30]. $I^2=74\%$ and a random-effects model was used. Results showed much lower incidence rates of POCD in the deep anesthesia group (BIS 30-50), compared to...
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Table 1. Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Age(yr)</th>
<th>Surgery</th>
<th>Anesthetic monitoring</th>
<th>Diagnostic method</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jian X [13]</td>
<td>40/40</td>
<td>45±7.93</td>
<td>Microvascular decompression surgery</td>
<td>BIS</td>
<td>Value Z</td>
<td>B</td>
</tr>
<tr>
<td>Matthew T.V</td>
<td>412/423</td>
<td>A: 61.8±8.2 B: 67.6±8.3</td>
<td>Elective surgery</td>
<td>BIS</td>
<td>Value Z</td>
<td>D</td>
</tr>
<tr>
<td>Jin LC [15]</td>
<td>50/50</td>
<td>A: 67.6±2.4 B: 68.7±2.8</td>
<td>Abdominal operation</td>
<td>NTI</td>
<td>MMSE</td>
<td>A, E</td>
</tr>
<tr>
<td>Bo H [16]</td>
<td>42/38</td>
<td>A: 70.2±8.3 B: 69.15±9.0</td>
<td>Noncardiac surgery</td>
<td>CSI</td>
<td>MMSE</td>
<td>A, C</td>
</tr>
<tr>
<td>Juan JJ [17]</td>
<td>116/137</td>
<td>A: 59±11.9 B: 68.3±9.2</td>
<td>General surgery operation</td>
<td>BIS</td>
<td>MMSE</td>
<td>A, B, C</td>
</tr>
<tr>
<td>Ling LL [18]</td>
<td>100/100</td>
<td>A: 68.4±2.6 B: 68.4±2.6</td>
<td>Abdominal operation</td>
<td>NTI</td>
<td>MMSE</td>
<td>A</td>
</tr>
<tr>
<td>Hui Z [19]</td>
<td>32/32</td>
<td>A: 51.9±8.7 B: 68.4±5.2</td>
<td>Gastrointestinal surgery</td>
<td>BIS</td>
<td>MMSE</td>
<td>A, B</td>
</tr>
<tr>
<td>Hong Z [20]</td>
<td>60/60</td>
<td>A: 67.2±7.3 B: 65.8±6.2</td>
<td>Elective laparoscopic surgery</td>
<td>BIS</td>
<td>SD</td>
<td>A, B, C</td>
</tr>
<tr>
<td>Cai LX [21]</td>
<td>20/20</td>
<td>A: &gt;40 B: &gt;40</td>
<td>Stomach cancer surgery</td>
<td>BIS</td>
<td>SD</td>
<td>A, B</td>
</tr>
<tr>
<td>An YJ [23]</td>
<td>51/51</td>
<td>A: 68.2±2.5 B: 67.5±2.6</td>
<td>Abdominal surgery</td>
<td>BIS</td>
<td>MMSE</td>
<td>A, E</td>
</tr>
<tr>
<td>Dong H [24]</td>
<td>30/30</td>
<td>A: 68±5 B: 67±5</td>
<td>Abdominal cancer surgery</td>
<td>BIS</td>
<td>MMSE</td>
<td>A, B</td>
</tr>
<tr>
<td>Jie YY [25]</td>
<td>40/40</td>
<td>A: 68.6±2.1 B: 68.0±2.3</td>
<td>Abdominal surgery</td>
<td>NTI</td>
<td>MMSE</td>
<td>A, E</td>
</tr>
<tr>
<td>Qing WD [26]</td>
<td>18/16</td>
<td>A: 69.6±2.41 B: 68.3±1.73</td>
<td>Abdominal surgical</td>
<td>NTI</td>
<td>MMSE</td>
<td>A, E</td>
</tr>
<tr>
<td>Fang S [27]</td>
<td>43/43</td>
<td>A: 73±8 B: 71±9</td>
<td>Gastrointestinal surgery</td>
<td>BIS</td>
<td>MMSE</td>
<td>A, B</td>
</tr>
<tr>
<td>Yin K [28]</td>
<td>49/96</td>
<td>A: 70.5±3.67 B: 71.9±5.18</td>
<td>Elective laparoscopic surgery for colorectal</td>
<td>NTI</td>
<td>Value Z</td>
<td>C</td>
</tr>
<tr>
<td>Nian L [29]</td>
<td>16/32</td>
<td>A: 60±7.0 B: 59.8±6.7</td>
<td>Elective laparoscopic surgery for colorectal</td>
<td>NTS</td>
<td>SD</td>
<td>C</td>
</tr>
<tr>
<td>Jia C [30]</td>
<td>53/54</td>
<td>A: 68.6±2.1 B: 68.0±2.3</td>
<td>Abdominal surgical</td>
<td>BIS</td>
<td>Unclear</td>
<td>C, D</td>
</tr>
<tr>
<td>Nan D [31]</td>
<td>36/35</td>
<td>60±80</td>
<td>Abdominal surgical</td>
<td>AAI</td>
<td>SD</td>
<td>C, D, E</td>
</tr>
<tr>
<td>Liang CY [32]</td>
<td>60/60</td>
<td>A: 69.6±7.1 B: 69.71±7.0</td>
<td>Elective laparoscopic surgery</td>
<td>BIS</td>
<td>Unclear</td>
<td>E</td>
</tr>
</tbody>
</table>

▲: Deep anesthesia group/Light anesthesia group; A: Incidence of POCD on postoperative day 1; B: Incidence of POCD from 3 to 5 days after surgery; C: Incidence of POCD on postoperative day 7; D: Incidence of POCD from 1 to 3 months after surgery; E: Serum S100-β protein levels on postoperative day 1; SD: standard deviation; MMSE: mini-mental state examination.

Effects of anesthetic depth on long-term POCD: Three RCTs (n=961) reported the effects of anesthetic depth on long-term POCD [14, 30, 31]. BIS values were used in all three RCTs. P=0 and a fixed-effects model was used, showing that deep anesthesia could reduce incidence of POCD more than light anesthesia from 1 to 3 months after surgery [OR, 0.66; 95% CI (0.45-0.99), P=0.04] (Figure 5). There was no significant publication bias, according to Egger’s testing (P=0.43).
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Effects of anesthetic depth on serum S-100β protein levels: Seven RCTs (n=686) studied the effects of anesthetic depth on serum S100-β levels on day 1 after surgery [15, 18, 22, 23, 25, 26, 32], with $P=0$. Results of fixed effects-model analysis showed that serum S100-β protein levels in the deep anesthesia group were much lower than those in the light anesthesia group (MD, -270.29; 95% CI (-295.81, -244.77), $P<0.00001$) (Figure 6). There was no obvious publication bias, according to the funnel plot (Figure 7).

Discussion

POCD is a common complication after surgery and anesthesia. Previous studies have shown that incidence rates of POCD are approximately 25% in the first week after surgery and approximately 10% after 3 months [33, 34]. Many factors, including patient age, sex, education levels, alcoholism, preoperative comorbidity, types of surgery, anesthesia, and postoperative infections, can induce or facilitate the development of POCD [4]. The current study analyzed the effects of anesthetic depth on POCD development. Results showed that deep anesthesia could reduce incidence of short or long-term POCD. The mechanisms may be that deep anesthesia can decrease cerebral oxygen metabolism, reduce perioperative stress, and inhibit the release of inflammatory cytokines, compared to light anesthesia. The boundary between deep and light anesthesia was based on the criteria in included trials. BIS 30-50, NTI 20-36, and AAI 20-30 were regarded as deep
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anesthesia. BIS 50-65, NTI 46-64, and AAI 30-40 were regarded as light anesthesia. Results of this meta-analysis showed that, when the BIS value was used, deep anesthesia (BIS 30-50) could reduce incidence of POCD on day 7 after surgery, compared with light anesthesia (BIS 50-65). However, when the NTI value was used, there were no differences between deep and light anesthesia. NTI values were only from 2 RCTs. The sample size was small. Furthermore, the methods used to diagnose POCD were different between these two trials. Burrow B [35] found that depth with a BIS value of 40-50 could facilitate patient rehabilita-
tion. However, other studies showed that the time that the BIS value was less than 45 was positively related to postoperative mortality [36, 37]. Therefore, choosing an appropriate anesthetic depth that can reduce POCD incidence and facilitate postoperative rehabilitation needs to be examined.

Current results suggest that deep anesthesia can reduce incidence of POCD from 1 to 3 months after surgery. A cohort study from Ehab et al. showed that deep anesthesia could facilitate recovery of POCD from 4 to 6 weeks after surgery, especially with the ability to process

Figure 4. Forest plot of effects of anesthetic depth with BIS and NTI monitoring on short-term POCD.

Figure 5. Forest plot of effects of anesthetic depth on long-term POCD.

Figure 6. Forest plot of effects of anesthetic depth on serum S100-β protein levels on postoperative 1 day.
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S100-β protein is secreted from glial cells in the central nervous system. This protein has a wide range of biological functions, including protecting neurons and promoting glial proliferation and differentiation, as well as playing an important role in learning and memory. Excessive expression of serum S100-β protein can lead to inflammatory response and dysfunction of neural cells [38]. Increasing serum concentrations of S100-β protein can reflect brain injuries [11]. Current meta-analysis results showed that deep anesthesia could attenuate the postoperative elevation of serum S100-β protein levels, which may be closely related to development of POCD.

The current study had some limitations. The methods for POCD diagnosis were not uniform in these included trials. Devices monitoring the depth of anesthesia, ages of the patients, surgical procedures, and anesthetic agents were also different, to some degree, in these trials. This may have affected short- or long-term POCD results. In addition, the sample size was not large enough. Prospective randomized trials with large sample sizes should be conducted in the future.

Conclusion

Deep anesthesia can significantly reduce incidence rates of short- or long-term POCD after surgery. It may also reduce serum S100-β protein levels on postoperative day 1. These levels may be closely related to development of short- or long-term POCD.

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Disclosure of conflict of interest

None.

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