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Original Contribution

The correlation of the depth of anesthesia and postoperative cognitive impairment: A meta-analysis based on randomized controlled trials

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ABSTRACT

Study objective and background: To comprehensively evaluate the associations between the depth of anesthesia and postoperative delirium (POD) or postoperative cognitive dysfunction (POCD).
Design: Using the Cochrane evaluation system, the included studies were conducted with quality assessment.
Data sources: We searched Cochrane library, Embase and PubMed databases without language restriction. The retrieval time is up to August 2017.
Eligibility criteria: According to the PRISMA guideline, the results associated with POCD and POD separately were compared between low and high bispectral index (BIS) groups under fixed effects model or random effects model. Besides, the risk ratio (RR) and 95% confidence intervals (95% CIs) were utilized as the effect sizes for merging the results. Furthermore, sensitivity analysis was performed to evaluate the stability of the results. Using Egger's test, publication bias was assessed for the included studies.
Results: Totally, 4 studies with high qualities were selected for this meta-analysis. The merged results of POCD showed no significant difference between low and high BIS groups (RR (95% CI) = 0.84 (0.21, 3.45), $P > 0.05$). Sensitivity analysis showed that the merged results of POCD were not stable (RR (95%CI) = 0.41 (0.17, 0.99)–1.88 (1.09, 3.22), $P = 0.046$). Additionally, no significant publication bias for POCD was found ($P = 0.385$).
Conclusion: There was no significant correlation between the depth of anesthesia and POCD.

1. Introduction

Perioperative cognitive impairment, including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), increases the mortality of patients [1,2]. There are many causes for POD and POCD, especially anesthesia is a risk factor that cannot be ignored [3]. In the process of operation, different depths of anesthesia have different effects for patients. Deep anesthesia is not conducive to patient's recovery and may threaten their life [4]. Whereas, light anesthesia will affect the surgical operation, and even creates long-term psychological trauma to patients who have intraoperative awareness [5].

Bispectral index (BIS) is one of the indicators for evaluating and monitoring the depth of anesthesia [6,7]. There are a series of clinical trials focusing on the correlation between the depth of anesthesia and postoperative cognitive impairment. For example, Chan et al. report that anesthesia guided by BIS permits dose reduction of anesthetic agents and thus reduces the rate of POD and POCD after surgery [8]. Weber et al. think that local anesthesia has beneficial influences on early postoperative neurocognitive functions in patients experiencing carotid endarterectomy (CEA) [9]. Anesthesia guided by auditory evoked potential (AEP) can lower anesthetic exposure and results in less early POCD and better cardiovascular stability [10,11]. The above researches have reported the association between the depth of anesthesia and POD and/or POCD, however, there exist conflicting findings in other studies. Bryson et al. compare general anesthesia with regional anesthesia, finding that no significant difference exists in the incidence of POCD or POD [12]. Mason et al. conclude that general anesthesia may lead to more POCD in relative to other anesthesia, but not for POD [13]. Compared with general anesthesia, intraoperative neuraxial anesthesia cannot reduce the risk of developing postoperative cognitive dysfunction [14]. However, a single research could not fully illustrate problems and bias might be caused by different researches. Therefore, we comprehensively assessed the association between the depth of anesthesia and postoperative cognitive impairment using the present meta-analysis.

2. Materials and methods

2.1. Search strategy

This meta-analysis was performed and reported according to the PRISMA guideline [15]. According to the predetermined strategies, the

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relevant studies were obtained from Cochrane library, Embase and PubMed databases, with the searching keywords of (delirium OR POCD OR cognitive OR cognition OR confusion OR confused OR (brain function monitoring)) AND ((bispectral index) OR BIS OR (depth of anesthesia)). The retrieval time is up to August 2017, without language restriction. Manual retrieval was also performed for paper documents, and the references of related reviews and included studies were further screened to obtain more appropriate studies.

2.2. Inclusion and exclusion criteria

Related studies were included based on the following criteria: (1) the subjects were adults who underwent surgical operations; (2) the research type was randomized controlled trial (RCT); (3) the patients were divided into low BIS and high BIS groups; (4) the outcomes were the risks of POD and POCD.

The exclusion criteria for this study included: (1) the study was involved with both BIS and other interventions (which could affect POD and POCD); (2) the research data could not be used for statistical analysis; (3) the studies were letters, reviews, comments, et al.; (4) for repeated publications or studies involving the data used for multiple researches, only the study with the most complete research information was included.

2.3. Data extraction and quality assessment

Two investigators searched literatures according to the above inclusion and exclusion criteria. After eligible studies were included, the following information was gained: publication time, the name of first author, geographic area, ages of the subjects, case numbers, and outcomes. Cochrane evaluation system includes the basic contents of allocation concealment, random sequence generation, blinding of outcome assessment, blinding of participants and personnel, selective reporting, incomplete outcome data and other bias, which can objectively and comprehensively evaluate all kinds of bias in studies [16]. Using the Cochrane evaluation system [16], quality assessment for the included studies was conducted. The disagreements during data extraction and quality assessment were resolved through discussion.

2.4. Statistical analysis

The risk ratio (RR) and 95% confidence intervals (95% CIs) were considered as the effect sizes for calculating the merged results. Using Cochran-based I^2 test and Q test [17], heterogeneity test was performed for the studies. When there was significant heterogeneity among the studies ($P < 0.05$, $I^2 > 50\%$), the random effects model was applied. On the contrary, the fixed effects model was used when homogeneous outcomes were obtained ($P > 0.05$, $I^2 < 50\%$). To evaluate the stability of the results, sensitivity analysis was conducted by removing one study each time. Based on Egger's test [18], publication bias existed among the included studies were assessed.

3. Results

3.1. Eligible studies

The flow chart showing the retrieved results and the process of study selection is displayed in Fig. 1. According to the predetermined strategies, 1271, 737 and 172 relevant studies were selected from PubMed, Embase and Cochrane library databases, respectively. After removing the repeated articles, 1916 studies were remained. A total of 1889 ineligible studies were eliminated after browsing tittle. Then, 14 studies were further removed through reading abstract. Furthermore, 9 studies were screened out following full-text reading. There were no eligible studies searched by manual retrieval. Finally, a total of 4 eligible studies were selected for this meta-analysis [19–22].

3.2. Study characteristics and quality assessments

As listed in Table 1, a total of 340 subjects (including 173 cases in low BIS group and 167 cases in high BIS group) were included into the present meta-analysis. The included studies were published from 2006 to 2016, which involved countries such as China and USA. The drugs that maintained the BIS levels were propofol or isoflurane. As shown in Fig. 2 and Fig. 3, the methodological bias of the included studies was relatively low, indicating the high qualities of the eligible studies.

3.3. Meta-analysis

A total of 3 literatures [19,20,22] reported POCD-associated results (Fig. 4). There were significant heterogeneity among the studies ($P = 0.004$, $I^2 = 81.9\%$), thus the random effects model was utilized to merge the results of POCD. The merged results suggested no significant difference between low BIS and high BIS groups (RR (95% CI) = 0.84 (0.21, 3.45), $P > 0.05$). Meanwhile, only 1 literature [21] covered the results of POD (RR (95% CI) = 2.09 (1.13, 3.88), $P = 0.019$) (Fig. 5).

3.4. Sensitivity analysis and publication bias

Through removing one study per time, we found that the merged results of POCD were not stable (RR (95%CI) = 0.41 (0.17, 0.99)–1.88 (1.09, 3.22), $P = 0.046$). Based on Egger's test, no significant publication bias was found for POCD ($P = 0.368$).

4. Discussion

In order to reduce the incidences of POD and POCD after surgery by controlling the doses of anesthetic agents, the association between the depth of anesthesia and postoperative cognitive impairment was fully analyzed in the current meta-analysis. According to the predetermined criteria, a total of 4 studies were eligible and thus were selected for this meta-analysis. Quality assessment showed that the eligible studies had high qualities. The merged results of POCD indicated no significant difference between low BIS

Table 1
The characteristics of the included studies.

Study	Year	Country	Surgery	Anesthesia medicine	Low BIS			High BIS			Outcome
					Age	n	M/F	Age	n	M/F	
An, J	2011	China	Facial surgery	Propofol	45.0 ± 7.93	40	17/23	48.8 ± 10.2	40	16/24	POCD
Farag, E	2006	USA	Spine, abdominal, pelvic	Isoflurane	63.8 ± 10.9	36	16/20	63.9 ± 9.6	38	18/20	POCD
Sieber, FE	2010	USA	Hip fracture repair	Propofol	81.8 ± 6.7	57	14/43	81.2 ± 7.6	57	17/40	POD
Valentin, LS	2016	USA	Noncardiac and nonneurologic surgery	Propofol	67.2 ± 5.2	40	19/21	68.7 ± 7.7	32	8/24	POCD

POD: postoperative delirium; POCD: postoperative cognitive dysfunction.