

## Original Article

# Effects of general anesthesia and non-general anesthesia on postoperative cognitive dysfunction in patients: a systematic review

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**Abstract:** Postoperative cognitive dysfunction (POCD) is a serious complication for patients undergoing surgery. Numerous studies have evaluated the effects of general anesthesia and non-general anesthesia on POCD. However, results have been inconsistent. Therefore, this systematic review was performed to further assess and analyze the effects of general anesthesia or non-general anesthesia on POCD. A comprehensive investigation was conducted to identify all eligible studies from online literature databases published before September 2017. A total of seven studies, with 1,031 patients, were included in this systematic review. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to examine the strength of association. Results showed significant differences in incidence of POCD between patients that underwent general anesthesia and those that underwent non-general anesthesia at 1 day and 3 days after surgery (OR = 3.86, 95% CI = 1.18-12.58,  $P = 0.03$ ), (OR = 2.00, 95% CI = 1.11-3.58,  $P = 0.02$ ). There were no remarkable differences in occurrence of POCD between patients with general anesthesia and non-general anesthesia at 7 days and 3 months after surgery (OR = 1.29, 95% CI = 0.84-1.98,  $P = 0.25$ ), (OR = 0.57, 95% CI = 0.17-1.85,  $P = 0.35$ ). This systematic review suggests that patients receiving general anesthesia had a higher incidence of POCD during the first 3 days after surgery. However, there were no differences between non-and general anesthesia after 7 days. Results suggest that early intervention should be performed on patients receiving general anesthesia.

**Keywords:** General anesthesia, postoperative cognitive dysfunction, meta-analysis

## Introduction

Postoperative cognitive dysfunction (POCD) is a common complication for patients that have undergone surgery. It is also a hot topic in anesthesiology and neurocognition research [1, 2]. The cerebral cortex is the basis of cognition. Any factors that cause functional abnormalities in the cerebral cortex can lead to cognitive dysfunction [3, 4]. Clinical manifestations of POCD can vary from mild cognitive abnormalities to severe memory impairment, such as loss of judgment and personality changes, considered the early stages of Alzheimer's disease (AD) [5]. If therapeutic intervention occurs at the stage of mild cognitive impairment, it might be possi-

ble to reduce incidence or delay the progression of AD [6, 7].

Age has been the only widely accepted risk factor for development of POCD [8]. However, there remain inconsistencies and controversies surrounding to what extent could anesthesia may affect incidence of POCD. Some studies have reported that general anesthesia might be the cause of POCD [9]. However, other studies have shown no significant differences in occurrence of POCD between patients receiving general and non-general anesthesia [10].

Currently, there are inconsistent conclusions regarding incidence of POCD between patients

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**Table 1.** Characteristics of studies included in the systematic review

Included studies	Number of patients	Patients with POCD
Casati A 2003 [11]	Spinal anesthesia/General Anesthesia (15/15)	Postoperative d 1, Spinal anesthesia/General Anesthesia (8/9) Postoperative d 7, Spinal anesthesia/General Anesthesia (1/3)
Williams-RP 1995 [12]	Epidural anesthesia/General Anesthesia (134/128)	Postoperative d 7, Epidural anesthesia/General Anesthesia (16/12)
Shi HJ 2015 [13]	Epidural anesthesia/General Anesthesia (50/50)	Postoperative d 1, Epidural anesthesia/General Anesthesia (8/18) Postoperative d 3, Epidural anesthesia/General Anesthesia (3/5)
Sun YB 2016 [14]	Epidural anesthesia/General Anesthesia (95/98)	Postoperative d 1, Epidural anesthesia/General Anesthesia (23/75) Postoperative d 3, Epidural anesthesia/General Anesthesia (21/36)
Silbert BS 2014 [15]	Spinal anesthesia/General Anesthesia (38/49)	Postoperative d 7, Spinal anesthesia/General Anesthesia (5/2) Postoperative m 3, Spinal anesthesia/General Anesthesia (9/3)
Zhang B 2012 [16]	Spinal anesthesia/General Anesthesia (15/30)	Postoperative d 7, Spinal anesthesia/General Anesthesia (0/4)
Rasmussen LS 2003 [17]	Regional anesthesia/General Anesthesia (158/156)	Postoperative d 7, Regional anesthesia/General Anesthesia (20/33) Postoperative m 3, Regional anesthesia/General Anesthesia (21/19)

receiving general and non-general anesthesia. Accordingly, the present study adopted the method of evidence-based medicine to strictly evaluate and analyze the effects of general and non-general anesthesia on incidence of POCD, performing an updated meta-analysis, providing evidence for clinical practice.

## Materials and methods

### Search strategy and inclusion criteria

Eligible studies in the Cochrane Library, PubMed, Medline, Web of Science, and other databases were searched. The above databases were searched from their inception dates up to September 2017. A combination of Medical Subheadings (MeSH) and free terms were used to retrieve all potential articles. Keywords used in the literature search included: “postoperative cognitive dysfunction” or “POCD” and “general anesthesia” and “epidural anesthesia” or “spinal anesthesia” or “nerve block or regional anesthesia”. Bibliographies of included articles were also searched to identify other potential studies. Three investigators worked independently, reviewing and evaluating all titles and abstracts to identify articles.

Articles were included in this systematic review according to the following criteria: (1) Studies had been published; (2) They were randomized controlled trials (RCTs); and (3) Patient ages  $\geq 18$  years old, no mental and neurological diseases, no history of anesthetic allergy, and all patients provided signed informed consent. Trials were excluded if the sample size was  $< 10$  and if the studies reported scientific meetings, correspondence, case reports, or review papers, duplicate publications, or contained incomplete information or data. In addition, animal studies and reviews were excluded.

### Data extraction

Three researchers independently reviewed the literature, according to inclusion and exclusion criteria. After obtaining full reports of the candidate trials, the same reviewers independently extracted all relevant information from all included studies using a standardized data collection form, checking the consistency of extracted data.

Cochrane Collaboration’s tool was used to assess risk of bias in the RCTs, which included seven items of risk bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).

### Statistical analysis

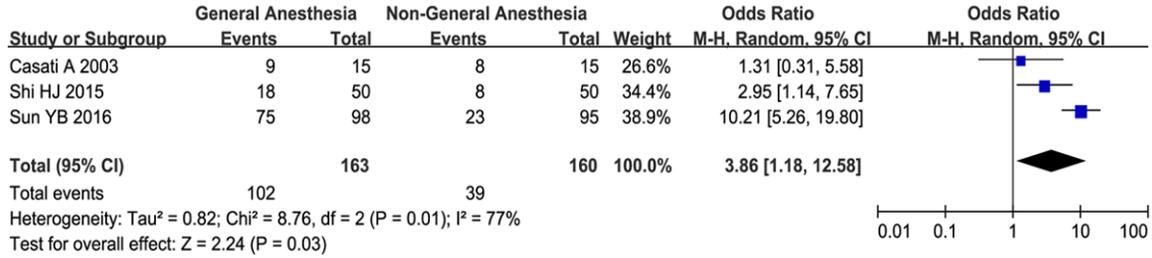
This systematic review was conducted using RevMan 5.2. Data are expressed as odds ratios (OR) and 95% confidence intervals (CI). Heterogeneity among studies was tested using  $I^2$  tests.  $P < 0.1$ ,  $I^2 \geq 50\%$  or  $P > 0.1$ ,  $I^2 > 50\%$  indicates the existence of heterogeneity. In this case, a random-effects model was used. A fixed-effects model was used to conduct the systematic review when there was no heterogeneity ( $P > 0.1$ ,  $I^2 < 50\%$  or  $P < 0.1$ ,  $I^2 < 50\%$ ).

## Results

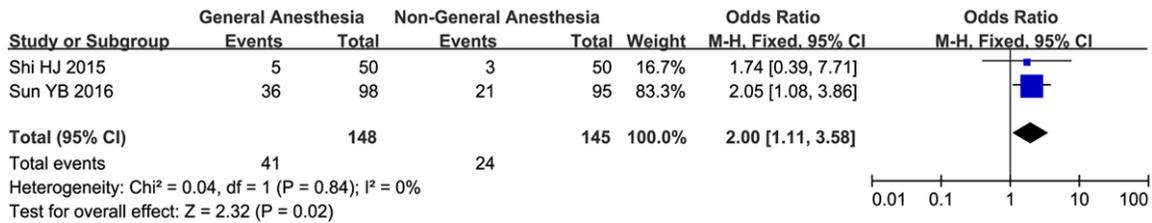
### Study characteristics

The search strategy identified 30 potentially relevant studies. According to inclusion criteria, a total of seven studies were finally included in the meta-analysis. A summary of included studies is shown in **Table 1**. The publication year of included studies ranged from 1995 to 2016.

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**Figure 1.** Forest plot of incidence of POCD the 1<sup>st</sup> day after surgery between patients that underwent general anesthesia and non-general anesthesia.



**Figure 2.** Forest plot of incidence of POCD the 3<sup>rd</sup> day after surgery between patients that underwent general anesthesia and non-general anesthesia.

Included studies included 1,031 patients in total, with 526 patients in the general anesthesia group and 505 patients in the non-general anesthesia group.

### *Incidence of POCD between general and non-general anesthesia at 1 day after surgery*

Three included studies [11, 13, 14] assessed incidence of POCD at 1 day after surgery between patients receiving general anesthesia and those receiving non-general anesthesia. A random-effects model was used for analysis due to heterogeneity among the studies. Results showed significant differences in incidence of POCD between general anesthesia and non-general anesthesia groups at 1 day after surgery (OR = 3.86, 95% CI = 1.18-12.58, P = 0.03) (**Figure 1**).

### *Incidence of POCD between general and non-general anesthesia at 3 days after surgery*

Two selected studies [13, 14] compared occurrence of POCD at 3 days after surgery. A fixed-effects model was used for analysis since there was no heterogeneity between the two studies. Results showed striking differences in occurrence of POCD at 3 days after surgery between general anesthesia and non-general anesthesia groups. (OR = 2.00, 95% CI = 1.11-3.58, P = 0.02) (**Figure 2**).

### *Incidence of POCD between general and non-general anesthesia at 7 days after surgery*

Five selected studies [11, 12, 15-17] evaluated incidence of POCD at 7 days after surgery. A fixed-effects model was used for analysis since there was no heterogeneity among the studies. Results showed no remarkable differences in incidence of POCD between the two groups at 7 days after surgery (OR = 1.29, 95% CI = 0.84-1.98, P = 0.25) (**Figure 3**).

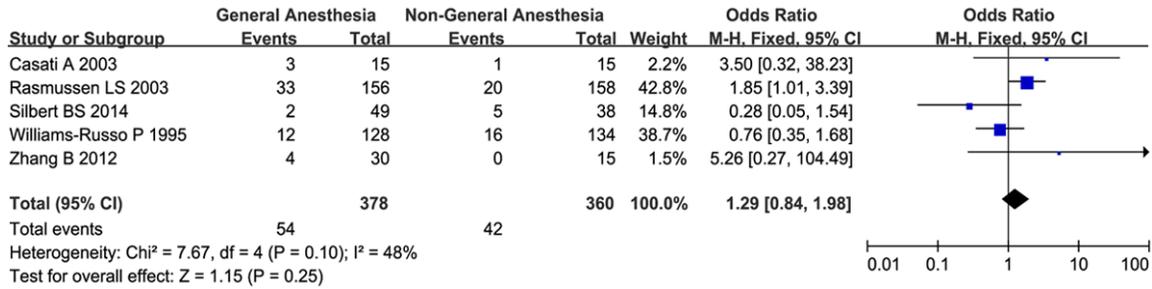
### *Incidence of POCD between general and non-general anesthesia at 3 months after surgery*

Two incorporated studies [15, 17] estimated occurrence of POCD at 3 months after surgery. There was heterogeneity between the studies, therefore, a random-effects model was used for analysis. Results showed no significant differences in occurrence of POCD between the two groups (OR = 0.57, 95% CI = 0.17-1.85, P = 0.35) (**Figure 4**).

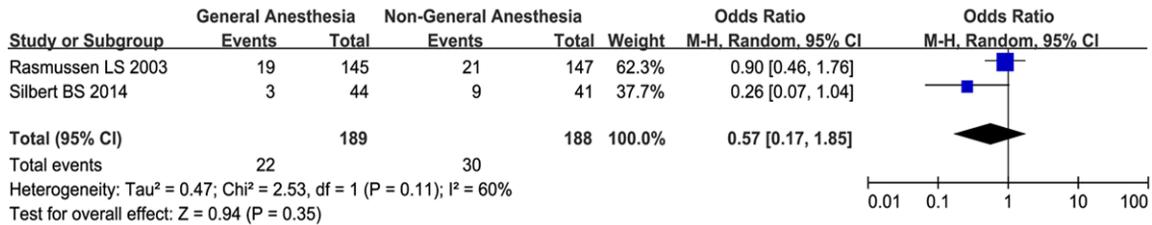
## Discussion

POCD is a neurodegenerative disorder which may be induced or aggravated by surgery, anesthesia, and many other factors [18]. POCD mainly manifests as insanity, anxiety, personality changes, memory impairment, and loss of self-care ability, which may result in further

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**Figure 3.** Forest plot of incidence of POCD the 7<sup>th</sup> day after surgery between patients that underwent general anesthesia and non-general anesthesia.



**Figure 4.** Forest plot of incidence of POCD the 3<sup>rd</sup> month after surgery between patients that underwent general anesthesia and non-general anesthesia.

deteriorative postoperative complications, prolonged duration of hospital stays, and increased social medical expenses [2, 19]. Therefore, clinicians should pay attention to occurrence of POCD in patients after surgery.

However, the pathogenesis of POCD is not completely clear. It might be related to increasing age, surgical trauma, narcotic drugs, disease types, stress response, and other factors [8, 20]. Notably, the relationship between narcotic drugs and incidence of POCD mainly manifests in the choice of anesthesia methods. There has been significant controversy about the relationship between different anesthesia methods and incidence of POCD.

The International study of postoperative cognitive dysfunction (IS-POCD) found that incidence of POCD was not significantly different between those receiving general anesthesia and those receiving spinal anesthesia in the elderly. However, patients receiving general anesthesia showed delayed responses to mental activity at 24 hours after surgery [21]. In addition, other studies have demonstrated that incidence of POCD in patients receiving general anesthesia was significantly higher than in those receiving spinal anesthesia [22]. Therefore, the choice of

an effective and appropriate anesthesia method might be crucial in preventing occurrence of POCD.

The present study compared incidence of POCD between patients receiving general anesthesia with those receiving non-general anesthesia. Results showed significant differences in incidence of POCD between the two groups of patients within 3 days after surgery. However, there were no significant differences in occurrence of POCD between the two groups of patients beyond 7 days after surgery.

Seven studies were included in this systematic review which used the Cochrane Collaborative Network System Evaluation to evaluate selected literature, ensuring the accuracy and reliability of analysis. In this study, mini-mental state examination (MMSE) or neuropsychological tests were used to assess the cognitive function of patients, which may have induced a risk of subjective bias risk. In addition, there were also some limitations in this systematic review. First, the number of included studies was low. Second, a possible language bias could have occurred because only English articles were included. Therefore, high-quality RCTs with larger numbers of samples are needed to further

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evaluate the effects of general anesthesia and non-general anesthesia on incidence of POCD in patients.

In summary, present results showed that both general anesthesia and non-general anesthesia could affect cognitive ability, leading to occurrence of POCD. Moreover, up to 3 days after surgery, incidence of POCD in patients receiving general anesthesia was higher than in those receiving non-general anesthesia. There were no significant differences between the two groups beyond 7 days after surgery. This study suggests that early intervention for patients at high-risk of POCD should be performed.

The outcomes of this study are credible, providing an evidence-based medicine reference for clinical practice. However, because of differences in anesthetization, medication, and basic physical features of patients from different countries and zones, the stability of results may have been affected. In addition, evaluating cognitive function during the first 3 postoperative days may be too early to reflect the actual incidence of POCD, as the effects of other factors, such as complications of postoperative infections and the use of benzodiazepine and opioids, might confuse the results of evaluation.

Therefore, the best time to assess cognitive function, before and after surgery, requires further investigation.

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### Disclosure of conflict of interest

None.

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