Meta-Analysis

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Effect of dexmedetomidine on postoperative cognitive dysfunction in elderly patients after general anaesthesia: A meta-analysis

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Abstract

Objective: We undertook a meta-analysis to investigate the effect of dexmedetomidine on postoperative cognitive dysfunction (POCD).

Methods: We searched PubMed, EMBASE, the Cochrane Library, CNKI and Google Scholar to find randomized controlled trials (RCTs) of the influence of dexmedetomidine on POCD in elderly adults who had undergone general anaesthesia. Two researchers independently screened the literature, extracted data, and evaluated methodologic quality against inclusion and exclusion criteria. We used RevMan 5.2 to undertake our meta-analysis.

Results: Thirteen RCTs were included. Compared with controls, dexmedetomidine: 1) significantly reduced the incidence of POCD (relative risk = 0.59, 95% confidence interval [CI] 0.45–2.95) and improved Mini-Mental State Examination (MMSE) score (mean difference, MD = 1.74, 95% CI 0.43–3.05) on the first postoperative day; and 2) reduced the incidence of POCD after the first postoperative day (MD = 2.73, 95% CI 1.33–4.12).

Conclusion: Dexmedetomidine reduces the incidence of POCD and improves postoperative MMSE score.

Keywords

Response: dexmedetomidine, general anesthesia, cognitive function, meta-analysis, RCT, POCD

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Postoperative cognitive dysfunction (POCD) is one of the most common complications affecting the central nervous system after general anaesthesia, especially in elderly patients. Its clinical manifestations include cognitive function disorder, personality change and memory impairment; in severe

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cases, Alzheimer's disease (AD) may occur. Postoperative cognitive dysfunction can prolong recovery from surgery and impair quality of life in the longer term. The Mini Mental State Examination (MMSE) is commonly used to evaluate cognitive function postoperatively. For patients over the age of 60 years, POCD can reportedly be identified in 25.8% of cases 1 week after surgery and in 9.9% of cases 3 months after surgery. Consequently, POCD has become a crucial concern for anaesthesiologists; however, the mechanism by which anaesthesia might provoke POCD and the influence of different modes of anaesthesia on the incidence of POCD remain unclear.

Dexmedetomidine, a highly selective $\alpha 2$ adrenoceptor agonist, mainly acts in the locus coeruleus to cause sedation. It also has analgesic properties. The use of dexmedetomidine in the conduct of anaesthesia for the elderly is becoming increasingly popular, as it has been reported to reduce the risk of POCD. Nevertheless, there is also a body of evidence that calls the efficacy of dexmedetomidine into question, and its role in anaesthesia for the elderly remains a matter of lively debate. We undertook a meta-analysis to examine the efficacy of dexmedetomidine for the prevention of POCD in elderly patients, so as to inform future clinical decision making.

Materials and methods

Inclusion and exclusion criteria

We identified randomized controlled trials (RCTs) of patients undergoing surgery under general anaesthesia. The intervention in the experimental group was a single or continuously-administered intravenous dose of dexmedetomidine before and during anaesthesia; the control groups received an intravenous injection of placebo. The main outcome indicator in eligible studies was the incidence of cognitive dysfunction on and after the first postoperative day, and MMSE score on the first postoperative day. We excluded studies that lacked specific exclusion data or with only figures and tables, duplicate publications, studies that used formulations of dexmedetomidine that are not widely available, studies with incomplete information or data, and articles for which we could not obtain the full text.

Search strategy

We searched PubMed, EMBASE, the Cochrane Library, China Academic Journals full-text database (CNKI) and Google Scholar to find relevant RCTs. For PubMed, a combination of subject terms and free text was adopted for the search thus: (''dexmedetomidine'' [MeSH Terms] OR ''dexmedetomidine'' [All Fields]) AND (''postoperative cognitive dysfunction'' [MeSH Terms] OR (''postoperative'' [All Fields] AND ''cognitive dysfunction'' [All Fields] OR ''postoperative cognitive dysfunction'' [All Fields] OR ''POCD'' [All Fields]) AND (''general anaesthesia'' [MeSH Terms] OR ''general anaesthesia'' [All Fields]). Search terms for other databases included ''dexmedetomidine'', ''postoperative cognitive dysfunction'', ''POCD'' and ''general anaesthesia''. The search dates ranged from the establishment of each database to June 2016.

Literature screening, data extraction and quality assessment

Two researchers independently screened the literature, extracted data and evaluated the methodologic quality of the studies identified. We evaluated methodologic quality of the RCTs identified using a modified Jadad scale. Evaluation included randomization, allocation concealment, and blinding of implementers and participants. The two researchers resolved disagreements by discussion or consulted a third party when consensus could not be reached. A data extraction

table was employed to extract data. Table 1 shows the extracted contents and Jadad scores.

Statistical analysis

We used RevMan 5.2 to conduct the meta-analysis. For dichotomous data, odds ratios (ORs) with 95% confidence intervals (CIs) were used to express effect-size, while mean difference (MD) and 95% CIs were used for continuous data. First, we conducted a heterogeneity test (significance level $\alpha = 0.10$) on included studies using the χ^2 test, and judged the extent of heterogeneity in combination with the I^2 test. A fixed effects model was used to conduct the meta-analysis if no heterogeneity ($P > 0.1$ and $I^2 < 50.0\%$) was found among the studies. If significant heterogeneity ($P \leq 0.1$ or $I^2 \geq 50.0\%$) was identified, we sought its source. For studies with significant clinical heterogeneity, subgroup or sensitivity analysis was employed, while for studies without distinct clinical heterogeneity, a random effects model was carefully applied for the meta-analysis.

Results

Literature search results

Initially, 564 relevant studies were identified; ultimately 13 RCTs were included in the meta-analysis.[1–13] The results of the literature screening process are shown in Figure 1.

Basic features and quality assessment of included studies

The characteristics of the included studies and the results of methodologic quality evaluation are presented in Table 1.

Meta-analysis results

Incidence of POCD. Ten RCTs reported the incidence of POCD on the first postoperative day. There was no substantial heterogeneity between the studies ($P = 0.60$, $I^2 = 0\%$). A fixed effect model was therefore adopted for meta-analysis, and the results showed that the incidence of POCD in dexmedetomidine group was significantly lower than controls (relative risk, $RR = 0.59$, 95% CI 0.45–0.76, $P < 0.0001$; Figure 2).

Seven RCTs reported the incidence of POCD after the first postoperative day. Again, we observed no substantial heterogeneity between the studies ($P = 0.36$, $I^2 = 9\%$). We therefore adopted a fixed effect model for meta-analysis, and found that there was no significant difference in the incidence of POCD between the dexmedetomidine and the control groups ($RR = 0.66$, 95% CI 0.45–0.98, $P = 0.04$; Figure 3).

Postoperative MMSE score. Six RCTs reported MMSE score on the first post-operative day. A random effects model was employed for meta-analysis, and the results suggested that MMSE was significantly higher on the first postoperative day in the dexmedetomidine group than the control group ($MD = 2.73$, 95% CI 1.33–4.12, $P < 0.00001$; Figure 4). However, we identified one study (Guo et al., 2015) that accounted for substantial heterogeneity. After this study was excluded from the analysis, the MD was determined to be 2.12, and sensitivity analysis identified 95% CIs of 1.30 to 2.95 ($I^2 = 43\%$).

Analysis of publication bias: Funnel plot analysis. The funnel plot was symmetrical, suggesting that there was no publication bias (Figure 5). Further subgroup analyses, on the basis of the types of surgery and surgical sites, had little effect on the pooled results.

Discussion

As societies age, more and more elderly patients are undergoing surgery, and are

Table 1. Characteristics of the studies included in the meta-analysis.

Author (publication year)	Headcount	Grouping	Surgical setting	Surgical site	Jadad score
Ding (2015)	100	Physiologic saline Dexmedetomidine	Laparoscopic radical prostatectomy	Prostate	5
Zhang (2014)	80	Physiologic saline Dexmedetomidine	Laparoscopic surgery	Colon and rectum	4
Li (2015)	100	Physiologic saline Dexmedetomidine	Laparoscopic cholecystectomy	Gall bladder	4
Mohamed (2014)	50	Physiologic saline Dexmedetomidine	Abdominal surgery	Abdomen	5
Chen (2015)	148	Physiologic saline Dexmedetomidine	Time-selection surgery	Fracture, prostate, gall bladder and rectal	3
Chen (2013)	122	Physiologic saline Dexmedetomidine	Laparoscopic cholecystectomy	Gall bladder	5
Guan (2015)	90	Physiologic saline Dexmedetomidine Ketamine	Laparoscopic surgery	Abdomen	4
Guo (2015)	149	Physiologic saline Dexmedetomidine	Cancer surgery	Oral	3
Li (2014)	180	Physiologic saline Dexmedetomidine	Abdominal surgery	Abdomen	3
Liu (2015)	88	Physiologic saline Dexmedetomidine	Elective surgery	Abdomen	3
Meng (2016)	40	Physiologic saline Dexmedetomidine	Laparoscopic surgery	Rectal	3
Peng (2012)	80	Physiologic saline Dexmedetomidine	Prostate resection	Prostate	
Zhang (2013)	120	Physiologic saline Dexmedetomidine Ketamine Dexmedetomidine + ketamine Ketamine	Orthopaedic surgery	Orthopaedic	3

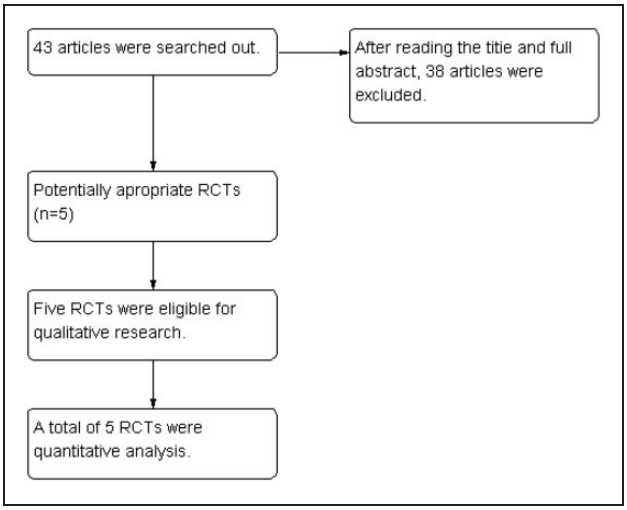

Figure 1. Study flow diagram.

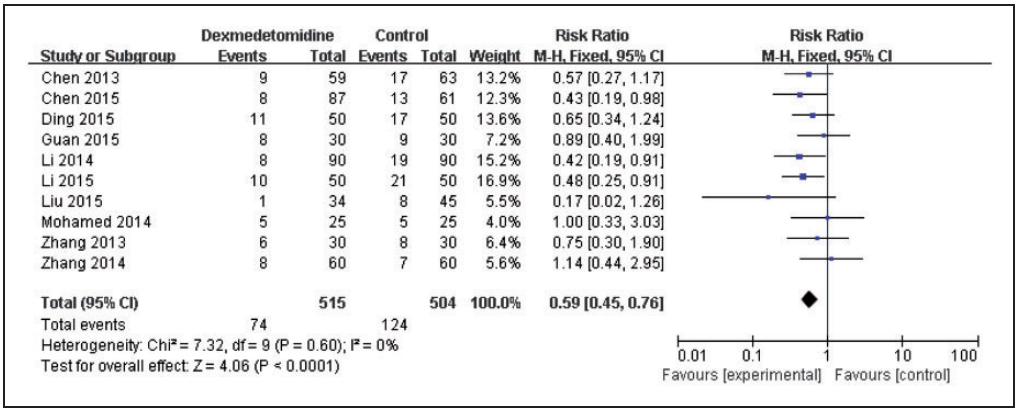

Figure 2. Incidence of POCD on the first post-operative day.

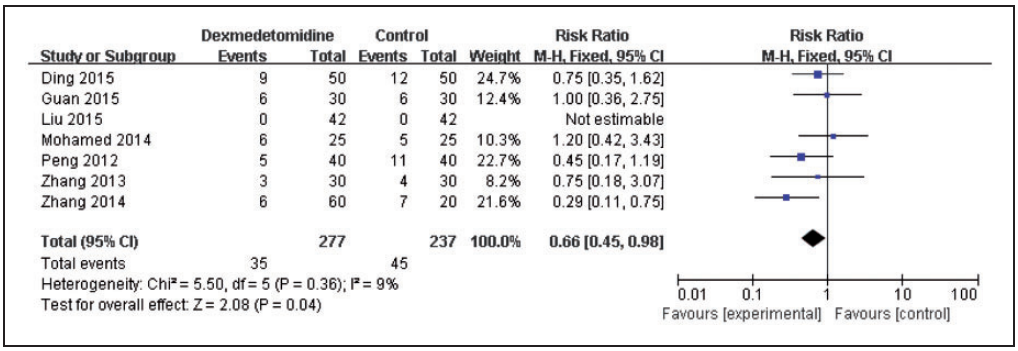

Figure 3. Incidence of POCD after the first post-operative day.

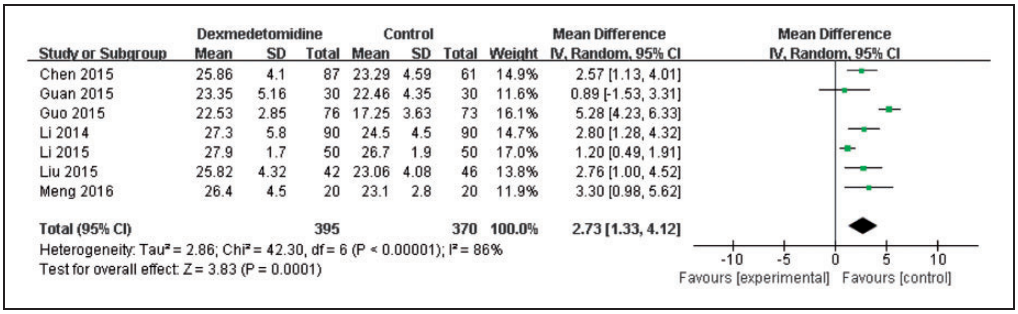

Figure 4. Mini-Mental State Examination score on the first post-operative day.

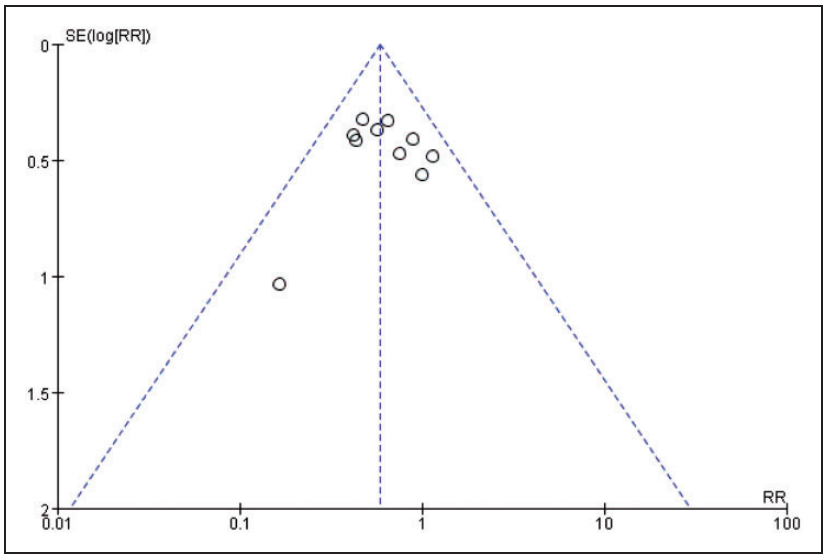

Figure 5. Funnel plot.

therefore exposed to the risk of POCD. The incidence of POCD in elderly patients is high, and there is increasing interest in identifying strategies to prevent POCD, given its consequences. The cause of POCD is still uncertain. Some investigators[14] have reported that the main symptoms of POCD include decreased memory and concentration, and degeneration of intelligence. Mild POCD may prolong hospitalization and increase the costs of care, but changes in memory, intelligence, verbal ability, personality and sociability and may impair patients' ability to engage with work and life activities. Severe POCD may cause patients to lose the ability to speak, bring about personality change and AD, and impair their capacity for self-care; the consequences for the quality of life of patients, their carers and society is profound.

Although POCD is common, its pathophysiologic mechanism is poorly understood. Several risk factors have, however, been identified, including duration of anaesthesia, need for reoperation, old age, postoperative infection, postoperative

respiratory complications and low educational level.[15]

Our meta-analysis suggested that dexmedetomidine can significantly reduce the incidence of early POCD in elderly patients and improve postoperative MMSE score. It acts at the locus coeruleus in the brain stem, which contains the highest concentration of α2 adrenoceptors. By regulating neurotransmitter release, the locus coeruleus is critical for coordination of waking and sleeping, and is the source of noradrenergic pathways from the medulla oblongata to the spinal cord. By acting on α2 adrenoceptors in the brain and spinal cord, dexmedetomidine inhibits neuronal discharge, thus inhibiting the effects of sympathetic nervous system activity. An association between POCD and the inflammatory response has also been reported. Cibelli and colleagues examined whether systemic inflammation in response to surgical trauma gives rise to subsequent memory impairment and hippocampal inflammation in a mouse model of orthopaedic surgery, and found that inflammation played a critical role in the pathogenesis of POCD and could be reversed by minocycline, a nonspecific inhibitor of inflammation.[16] The trauma of surgery stimulates the immune cascade and the release of inflammatory mediators, which may then provoke POCD. A number of animal experiments have shown that dexmedetomidine can reduce inflammation,[17,18] which may also explain how it reduces the incidence of POCD.

Dexmedetomidine can reduce cerebral blood flow by reducing cerebral perfusion pressure, and even during hyperventilation, also can reduce cerebral oxygen saturation without affecting oxygen supply to the brain. Furthermore, it can act as a neuroprotectant in areas of localized cerebral ischemia or tissue hypoxia.[19]

There is a body of opinion that POCD is provoked by intraoperative arterial hypotension, excessive doses of anaesthetic drugs and increased serum cortisol concentration.[20] Dexmedetomidine, when administered as an adjunct to anaesthesia, promotes hemodynamic stability,[21,22] while reducing the dose of intraoperative anaesthetic and analgesic drugs.[22,23] These properties could also explain its therapeutic benefits in preventing POCD.

Sato et al.[24] reported that dexmedetomidine confers its neuroprotective effects by mitigating injury to neurons in the hippocampal CA1 region in a rat model of cerebral ischemia. In neonatal rats,[25] dexmedetomidine can improve postanaesthetic neurocognitive function by diminishing isoflurane-induced injury to the hippocampus, thalamus and cortex. Several other previous studies also have reported this phenomenon in rodents.[26–28] If isoflurane-induced neuroapoptosis emerges as a problem in clinical practice, co-administration of dexmedetomidine with isoflurane may reduce neurotoxicity.

Although factors associated with anaesthesia and surgery have both been identified as risk factors for POCD, little is known about surgery-related causes. Only cardiac surgery has been identified as a risk factor, and there is no strong evidence that other surgical procedures or techniques influence the incidence of POCD. In contrast, regional anaesthesia is associated with a reduced incidence of POCD compared with general anaesthesia.

Our study had some limitations. The number of studies and the combined sample size were relatively small, and the doses and methods of administration of dexmedetomidine given to patients varied substantially. The included studies' inclusion and exclusion criteria, and consequently the characteristics of the patient cohorts, were also varied, which might have resulted in heterogeneity.

In summary, dexmedetomidine appears to reduce significantly the risk of early POCD in elderly patients after general anaesthesia, and improve postoperative MMSE score.

Author Contributions

Conception and design of the study: Chengmao Zhou, Yu Zhu, Lin Ruan. Search strategy: Chengmao Zhou, Yu Zhu, Zhen Liu, Lin Ruan. Data analysis: Chengmao Zhou, Yu Zhu, Lin Ruan. Contributed materials or analysis tools: Chengmao Zhou, Yu Zhu, Lin Ruan. Wrote the paper: Chengmao Zhou, Yu Zhu, Zhen Liu, Lin Ruan.

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Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

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