Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: A meta-analysis of randomized controlled trials

Peng Li
Changhai Hospital Department of Anesthesiology

Lu-xi Li
Changhai Hospital Department of Anesthesiology

Zhen-zhen Zhao
Changhai Hospital Department of Anesthesiology

Jian Xie
Changhai Hospital Department of Anesthesiology

Cheng-long Zhu
Changhai Hospital Department of Anesthesiology

Xiao-ming Deng
Changhai Hospital Department of Anesthesiology

Jia-feng Wang (jfwang@smmu.edu.cn)
Changhai Hospital, Second Military Medical University  https://orcid.org/0000-0002-1368-3061

Research Article

Keywords: dexmedetomidine, delirium, cardiac surgery

DOI: https://doi.org/10.21203/rs.3.rs-301490/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background

The role of dexmedetomidine in preventing delirium after cardiac surgery remains controversial because of several recent trials with negative results. We aimed to perform an updated meta-analysis of randomized controlled trials (RCTs) to clarify this controversy.

Methods

RCTs investigating the perioperative administration of dexmedetomidine in cardiac surgery were retrieved from PubMed, Web of Science, and the Cochrane library until August 27, 2020. Two researchers independently screened the literature, collected the data and evaluated the bias risk of the included studies. The meta-analysis was performed with the RevMan 5.3.

Results

A total of 15 studies including 2813 patients were included in the study. A pooled result showed that dexmedetomidine could reduce the risk of delirium in adult population underwent cardiac surgery (OR 0.56, 95% CI 0.35–0.89, P = 0.0003, I² = 64%). The subgroup analysis demonstrated that the protective effect of dexmedetomidine was only present in the patients injected with dexmedetomidine after surgery but not from the start of surgery, in the adult patients without specific age limitation but not in the elderly, and in the studies in comparison with other sedatives but not with placebo. There were no statistical differences when analyzing the secondary outcomes including hypotension (OR 1.13; 95% CI 0.54–2.37, P < 0.00001, I² = 85%), bradycardia (OR 1.72; 95% CI 0.84–3.53, P = 0.04, I² = 58%) and atrial fibrillation (OR 0.87; 95% CI 0.70–1.08, P = 0.43, I² = 0).

Conclusions

Dexmedetomidine can reduce the incidence of delirium compared to other sedatives and opioids after cardiac surgery in adult patients. The proper population and timing for perioperative use of dexmedetomidine after cardiac surgery remain to be further investigated.

Background

Dexmedetomidine is an acute brain disorder that involves changes in consciousness, attention, cognition, and perception. The incidence of postoperative delirium is high among patients undergoing cardiac surgery, ranging from 20–50%, and the risk is even higher in the elderly. Delirium may lead to undesirable outcome for the patients and their families, and is associated with increasing nursing home admission, elevated healthcare costs, high morbidity and mortality.

Although the risk factors and consequences of delirium are well recognized, no pharmacologic agent has been approved to treat this disorder. Several recent meta-analyses of randomized clinical trials have found that dexmedetomidine reduces the incidence of delirium in patients after cardiac surgery. However, several recent well-designed large-scale randomized controlled trials failed to find a beneficial effect of dexmedetomidine in preventing delirium after cardiac surgery. Therefore, we performed an updated meta-analysis of randomized controlled trials to explore the pooled effects of dexmedetomidine in patients undergoing cardiac surgery with inclusion of the recent trials with negative results.

Methods

Protocol and registration

This meta-analysis was conducted in accordance with the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search strategy

Search strategy

Relevant researches published from inception of databases until August 27, 2020 were systematically searched by the following databases: Pubmed/Medline, the Cochrane Library/Central, Embase and Web of science. The references included in the study were also reviewed. According to the search strategy, both MeSH terms and free terms were used. A basic search strategy was conducted using the following terms: (dexmedetomidine OR “dexmedetomidine” [MeSH]) AND (“cardiac surgery” OR “heart surgery” OR valve OR CPB OR “cardiopulmonary bypass” OR CAB OR “coronary artery bypass” OR “aortic surgery” OR “congenital heart disease”) in All Fields. Then those studies were screened for delirium in the outcome.

Inclusion and exclusion criteria

Inclusion criteria for this study were as follows: each study contained two comparison groups, one received dexmedetomidine, and the other group received normal saline (NS) or other anesthetic drugs. Delirium should be included in the primary or secondary outcome. Only randomized controlled trials and those published in English language were included to ensure the quality of pooled results.

Pediatric surgery, non-cardiac surgery, non-intravenous administration of dexmedetomidine, retrospective study, observational study, reviews and animal studies were excluded. The articles that failed to provide sufficient information or data were also excluded.
Endpoints

The primary endpoint of this meta-analysis was the incidence of delirium after cardiac surgery at any time during a patient's hospital stay, and Delirium was measured by the Confusion Assessment Method (CAM), CAM-ICU or RASS. The secondary outcomes included the incidence of bradycardia, hypotension and atrial fibrillation in ICU.

Data extraction

Data extraction and quality assessment were completed by 2 authors independently and all the information were summarized into a table. The differences in data extraction and quality assessment were discussed and subjected to a third reviewer if no agreement was obtained. The extracted data and information included first author, published year, surgery type, the duration of cardiopulmonary bypass (CPB), timing and dose of dexmedetomidine and the control group and methods of delirium assessment methods. The adverse events including bradycardia hypotension and atrial fibrillation were extracted as well.

Quality assessment

Quality assessment of included RCTs was performed according to the Cochrane bias risk assessment tool. The criteria were composed of the randomization method, allocation concealment blind of researchers and subjects, blinding to the outcome assessment, incomplete outcome reporting, selective reporting and others.

Statistical analysis

Meta-analysis was performed using the RevMan 5.3 software to present the dichotomous data (incidence of delirium, bradycardia, hypotension and atrial fibrillation). The odds ratio (OR) with a 95% confidence interval (CI) was used to represent the effects of intervention over that of control. The heterogeneity test was evaluated by the I² coefficient. An I²> 75% suggested an obvious heterogeneity between the studies; if the I²<40%, the study could be considered homogeneous; if the I² was between 30–60%, a moderate heterogeneity was considered. According to the results of the heterogeneity calculation, the random effect model was used if there was significant heterogeneity; otherwise, the fixed effect model was used. When significant heterogeneity was indicated, the subgroup analysis of the target data was introduced. The results of meta-analysis were presented in forms of forest plots. And the funnel plot was used to detect publication bias. All significance testing was two-sided, and P < 0.05 was considered as statistically significant.

Results

Search results and characteristics of included studies

According to the search strategy, a total of 930 trials were retrieved. Among them, 780 studies were removed because of non-randomized design. The other 150 studies were screened strictly based on the inclusion and exclusion criteria, and 129 of them were discarded due to no relevance to delirium. Finally, 15 RCTs including 2813 patients were ultimately included in this meta-analysis. The flow diagram following the PRISMA guideline was shown in Fig. 1. All the included articles were evaluated with the quality assessment items of Cochrane Risk of Bias Methods. Four trials were evaluated as high risk of performance bias and the others were defined as good qualities (Fig. 2). The major characters of these included studies were extracted and presented in Table 1. There were 1405 patients receiving dexmedetomidine and 1408 receiving control. The control included normal saline in 5 studies[9, 12–15], propofol in 5 studies[4, 10, 16–18], opioid in 4 studies[19–21], and midazolam combined with propofol in 1 study[22].
Table 1  
The major characters of these included studies.

| Studies    | Publish year | sample size (n) | Age (yr) | Type of surgery | Dexmedetomidine doses | Control | Delirium assessment methods | Time of CPB (min) | Primary Outcomes | Secondary Outcomes |
|------------|--------------|-----------------|----------|-----------------|-----------------------|---------|-----------------------------|------------------|------------------|-------------------|
| Azeem      | 2018         | 60              | *DEX*: 65.3 ± 4.8 | MIX | infusion 0.4–0.7 µg/kg/h postoperatively | MOR | CAMICU | ND | Delirium incidence | HR, SBP, DB Duration of intubation & mechanical ventilation |
| Con: 66.7 ± 5.6 | | | | | | | | | | |
| Balkanay   | 2015         | 88              | Mean age: 60.5 ± 8.6 | CABB | High-dose DEX group: 0.04–0.50 mg/kg/h | NS | ND | NS: 91.1 ± 32.1 | Renal function | Delirium incidence, length of ICU stay, hospital stay, bradycardia, hypotension, AF, postoperative agitation, furosemide need |
| Corbett    | 2005         | 89              | DEX: 63.6 ± 10.1 | CABB | 1mg/kg loading dose, then 0.4 mg/kg/h during MV | PRO | Modified Hewitt questionnaire | ND | Patients’ satisfaction | Delirium incidence, length of ICU stay, hospital stay, MV, inhospital mortality, etc |
| Djaiani    | 2016         | 183             | DEX: 72.7 ± 6.4 | MIX | 0.4 µg/kg infusion over a period of 10-20 min followed by 0.2–0.7 µg/kg/h infusion | PRO | CAM and CAM-ICU | DEX: 100 (71–127) | Delirium incidence | Delirium duration, length of ICU stay, hospital stay, time to extubation, hospital mortality, Al etc |
| Li         | 2017         | 285             | DEX: 66.4 ± 5.4 | MIX | 0.6 µg/kg infusion for 10 minutes, then 0.4 µg/kg/h until the end of surgery, 0.1 µg/kg/h after surgery | NS | CAM and CAM-ICU | DEX: 105 (84 to 129) | Delirium incidence | Delirium duration, length of ICU stay, hospital stay, MV, 30 day mortality, bradycardia etc |
| NS: 67.5 ± 5.3 | | | | | | | NS: 101 (81 to 130) | Delirium incidence, bradycardia hypotension, nausea, vomiting, Al etc |
| Liu        | 2016         | 61              | DEX: 53 (48–63) | Cardiac valve surgery | 0.2–1.5 mg/kg/h after arrival on ICU before extubation | PRO | CAMICU | 73 (60–88) | microcirculatory variables and clinical parameters | Delirium incidence, bradycardia hypotension, nausea, vomiting, Al etc |
| PRO: 55 (48–62) | | | | | | | PRO: 68 (54–80) | Delirium incidence, bradycardia hypotension, nausea, vomiting, Al etc |
| Maldonado  | 2009         | 90              | DEX: 55 ± 16 | Cardiac valve surgery | Loading dose: 0.4µg/kg, followed by a maintenance drip of 0.2 ug/kg/h–0.7ug/kg/h | PRO and MID | Diagnostic and Statistical Manual of Mental Disorders | DEX: 165 ± 62 | Delirium incidence | Length of stay in ICU and hospital, use postoperative rescue medication: |
| MID: 60 ± 16 | | | | | | | MID: 163 ± 51 | Delirium incidence | Length of stay in ICU and hospital, use postoperative rescue medication: |

DEX, dexmedetomidine; NS, normal saline; REM, remifentanil; MOR, morphine; PRO, propofol; MID, midazolam; CAM, Confusion Assessment Method; CAM-ICU CAM for Intensive Care Unit; RASS, Richmond Agitation Sedation Scale; MV, mechanical ventilation; CPB, cardiopulmonary bypass; CABB, coronary artery bypass grafting; DEX1, Total dose of Dex < 8µg/kg group; DEX2, Total dose of Dex ≥ 8µµg/kg group; MIX, Mixed cardiac surgery; AF, atrial fibrillation; ND, No Data.
| Studies   | Publish year | Sample size (n) | Age (yr) | Type of surgery | Dexmedetomidine doses | Control | Delirium assessment methods | Time of CPB (min) | Primary Outcomes | Secondary Outcomes |
|-----------|--------------|----------------|----------|-----------------|----------------------|---------|----------------------------|------------------|-----------------|-------------------|
| Massoumi  | 2019         | 88             |          | DEX: 61.80 ± 7.90 | CABG: DEX 1 µg/kg subcutaneously treated within 10 minutes and 0.2–0.7 µg/kg/h in hour infusion by the syringe pump | NS      | RASS CAM-ICU               | ND               | Delirium incidence | Laboratory variables or vital signs |
| Park      | 2014         | 142            |          | DEX: 51.09 ± 16.10 | MIX: DEX 0.5 mg/kg loading dose after arrival on ICU, then 0.2–0.8 mg/kg/h until discharged from ICU | REM     | CAM-ICU                   | DEX: 159.55 ± 56.55 REM: 173.19 ± 79.56 | Delirium incidence | Delirium duration, length of ICU stay, hospital stay time to extubation, bradycardia |
| Priye     | 2015         | 64             |          | DEX: 45.1 ± 14.7 | MIX: DEX 0.4 mg/kg/h arrival on ICU for 12 h | NS      | RASS                       | DEX: 98.22 ± 30.61 NS: 95.00 ± 35.51 | VAS scores       | Delirium incidence, awakening time |
| Shehabi   | 2009         | 299            |          | DEX: 71.5 (66 to 76) | MIX: DEX 0.1–0.7 mg/kg/h until removal of chest drain | MOR     | CAM-ICU                   | DEX: 98 (80 to 128) MOR: 100 (77 to 120) | Delirium incidence | Length of stay in ICU and hospital, time to extubation in-hospital mortality, bradycardia hypotension tachycardia AF, VF, etc |
| Shi       | 2019         | 164            |          | DEX: 74.7 ± 7.2 | MIX: DEX 0.4–0.6 µg/kg/h maintenance syringe pump intravenous infusion during operation | PRO     | CAM                        | DEX: 110.8 (25.2) PRO: 115.1 (28.9) | Delirium incidence | Delirium on Delirium duration, length of stay in ICU and hospital |
| Shokri    | 2019         | 286            |          | DEX: 63.75 ± 3.29 | CABG: DEX 0.7–1.2 µg/kg/h with an increment of 0.1–0.2 µg/kg/h every 30 min, up to 1–1.4 µg/kg body weight/h | Clonidine | CAM-ICU                   | ND               | Delirium incidence | Extubation time, length of intensive care unit (ICU and hospital) need for inotropic support or vasopressor |
The timing of dexmedetomidine was classified into perioperative use and postoperative use according to the start time of administration. The timing was started from before or after anesthesia induction in the operating room in 5 studies [9, 14, 16, 18, 22] and started chest closure maintained until the end of mechanical ventilation or continued for 24 h in ICU in the rest of included studies [4, 10, 12, 13, 15, 17, 19–21, 23].

The surgery type included coronary artery bypass grafting (CABG) in 4 trials [13, 15, 18, 20], valve surgery in 2 trials [17, 22] and mix surgery (CABG and valve surgery) in 9 studies [4, 9, 10, 12, 14, 16, 19, 21, 23]. Delirium incidence was set as the primary outcomes in most of the studies [4, 9, 10, 13, 14, 16, 19–23], while in 4 trials it was chosen as the secondary outcomes [12, 15, 17, 18].

### Primary outcome: incidence of postoperative delirium

This meta-analysis revealed that dexmedetomidine can significantly decrease the incidence of postoperative delirium compared to the controls (OR 0.56, 95% CI 0.35–0.89, P = 0.0003, I²=64%; Fig. 3). Dexmedetomidine reduced the risk of delirium by 44%. Funnel plot for the total POD incidence did not suggest the significantly presence of significantly publication bias (Fig. 4).

Then we performed a subgroup analysis to find potential sources of heterogeneity and evaluate the risk factors influencing postoperative delirium. We divide the studies according to potential associated factors, including age (patients older than 65 years or not) (Fig. 5), timing of administration (postoperative only or both intra-and postoperative) (Fig. 6), different controls (normal saline or other anesthetic drugs) (Fig. 7). The subgroup analysis of age showed that dexmedetomidine reduced the delirium incidence only in adult population without age restriction, but not in the elderly population (Fig. 5). When the studies were divided according to the timing of administration, it was demonstrated that the incidence of delirium was reduced in studies in which dexmedetomidine was administered after surgery, but not in those with intraoperative use (Fig. 6). Interestingly, dexmedetomidine was favored in preventing delirium when compared to other sedatives, but not to normal saline (Fig. 7).

### Secondary outcomes: complications

In the 15 studies included in the meta-analysis, 7 studies compared the incidence of postoperative hypotension, but the data was too heterogenous to be pooled though the trend showed a negative result (OR 1.13, 95% CI 0.54–2.37, P < 0.00001, I²=85%) (Fig. 8). The incidence of postoperative bradycardia was compared in 6 studies but no statistical difference was identified (OR 1.72, 95% CI 0.84–3.53, P = 0.04, I²=58%) (Fig. 9). Atrial fibrillation was reported in 7 studies but no significant difference was found either (OR 0.87; 95% CI 0.70–1.08, P = 0.43, I²=0) (Fig. 10).

### Discussion

Our meta-analysis demonstrates that dexmedetomidine can decrease the incidence of delirium for adult patients after cardiac surgery, although several recent large-scale trials with negative results were included [9]. The protective effect of dexmedetomidine against postoperative delirium after cardiac surgery does not seem to be shown in the elderly population. The subgroup analysis also suggests that the ideal time for administering dexmedetomidine may be postoperative period, but not from intraoperative to postoperative period. Most interestingly, dexmedetomidine may reduce the incidence of postoperative delirium only when compared to other anesthetics, but not to normal saline. The secondary analyses show that there is no significant difference in
complications associated with dexmedetomidine infusion, such as bradycardia, hypotension and atrial fibrillation. But the number of the included trials may not be large enough to confirm the results of secondary analyses.

The main result of this meta-analysis is not surprising because previous meta-analyses have provided strong evidence for dexmedetomidine in preventing delirium after cardiac surgery.[7, 8] But one very recent, large-scale, randomized controlled trial with negative result raised new doubt in the protective effect of dexmedetomidine[9]. The effect of dexmedetomidine against delirium might have not been fully clarified. Therefore, we performed the subgroup analyses to investigate the factors influencing the protective of dexmedetomidine against delirium after cardiac surgery.

The subgroup analyses seemed to show that dexmedetomidine was not protective against postoperative delirium in all of the patients undergoing cardiac surgery. Age and the time to start administration were two important factors determining the positive effect of preventing postoperative delirium. Although the age is a risk factor for postoperative delirium, dexmedetomidine failed to reduce the incidence of postoperative delirium after cardiac surgery. However, in non-cardiac surgery, it favors administering dexmedetomidine to prevent delirium in an RCT with a relatively large sample size and a previous meta-analysis[24, 25]. The different hemodynamic status between cardiac surgery and non-cardiac surgery might be one of the reasons. Hypotension might be more frequent in cardiac surgery, and especially in the elderly undergoing cardiac surgery[26, 27]. Intraoperative hypotension is a risk factor for postoperative delirium, and dexmedetomidine may induce intraoperative hypotension, which was not well recorded in most of the clinical trials[26, 27]. Thus, the hypotension induced by dexmedetomidine might be the reason why delirium was not protective in the elderly in this meta-analysis[28]. It is interesting to notice that the protective effect was shown in postoperative use of dexmedetomidine, but not the use from intraoperative to postoperative period. Anesthesia depth has been reported to be associated with postoperative delirium and dexmedetomidine might induce deeper anesthesia depth[26, 28]. But further studies were required to investigate these speculations.

However, the role of arterial blood pressure abnormalities in postoperative delirium during cardiac surgery remains unclear[26, 27, 29, 30]. Research on the issue has focused on low blood pressure, but with conflicting results[26, 27, 29, 30]. It has been suggested that delirium may be associated with high flow and cerebral perfusion during CPB in excess of cerebral metabolic requirements, resulting in excessive brain micro-emboli load, endothelial cell damage, and damage to the blood-brain barrier, leading to cerebral edema, and thereby brain dysfunction[29, 30]. In summary, existing studies suggest an increased risk of postoperative delirium in a small number of patients with chronic or deep hypotension, but this risk is not statistically significant[31]. Further studies are needed to confirm the effect of blood pressure management on the incidence of delirium. In addition, a study of rats showed that blood transfusions increase interleukin-6 levels and lead to neuroinflammation and subsequent cognitive impairment[32].

Sedation with anesthetics or analgesics are common in the intensive care unit (ICU) to allow the patient to remain comfortable, calm, and painless[33]. Sedation and analgesia are required in most of the intensive situations to promote natural sleep, facilitate assisted ventilation, and regulate physiological responses to stress (such as tachycardia and hypertension). The commonly used sedative medications include propofol, morphine, dexmedetomidine, clonidine and benzodiazepines[6]. Compared with propofol, the anti-sympathetic action of dexmedetomidine reduces serum catecholamine, lowers heart rate, increases blood supply to the coronary arteries of the left ventricle by extending diastolic duration and reduces myocardial oxygen consumption[34]. The risk of side effect such as hypotension or vasopressin requirement induced by dexmedetomidine is lower than that induced by other anesthetics or analgesics[34]. Although the secondary analysis suggested that dexmedetomidine did not alter the incidence of postoperative hypotension, but the data was too heterogenous to be pooled. The type of control medication or the frequency of monitoring might also confound the explanation of this result. Thus, we speculated that dexmedetomidine might result in less hemodynamic events and non-physiological sleep, which might be associated with delirium.

Our data suggested that dexmedetomidine did not reduce the incidence of delirium compared with normal saline but it did prevent postoperative delirium when compared to other anesthetics or analgesics. Therefore, when sedation must be performed, dexmedetomidine might be a better choice than other anesthetics or analgesics.

On the other hand, 5 studies were included in the subgroup analysis of control medication, but according to the sample size of these studies, the study performed by Turan et al.[9] contributed the most weight in this sub-analysis and it might also be one of the important reasons why our meta-analysis demonstrated that dexmedetomidine was not protective against postoperative delirium after cardiac surgery in comparison to placebo. In the study of Turan et al., anesthesiologists and intensivists were allowed to decrease the dose of dexmedetomidine and other sedatives were allowed to be used when necessary. But the cumulative dose of dexmedetomidine and other sedatives were not quantified, thus we were unable to assess whether patients in the dexmedetomidine group received more sedatives. The increased dose of sedatives might also contribute to the negative result in this study. Therefore, the effect of dexmedetomidine in preventing postoperative delirium compared to placebo needed to be further investigated in future randomized controlled studies.

**Limitations**

There are several potential limitations in our study. Firstly, several recent RCTs with negative results have a significant influence on the heterogeneity of this meta-analysis, especially the one published in 2020 [9] which is outside the funnel plot. Secondly, the present study did not investigate the incidence of organ injury, so it was not possible to demonstrate whether dexmedetomidine was worthy to be used in cardiac surgery from this perspective. Thirdly, in this study, we also did not involve the analyses regarding intraoperative blood pressure, BIS value and other indicators clearly affecting postoperative delirium, because many studies did not report these data. Therefore, it is not clear whether strict management of hemodynamic status and anesthetic depth would influence the benefit of dexmedetomidine in preventing postoperative delirium.

**Conclusion**
In summary, postoperative infusion of dexmedetomidine can reduce the incidence of postoperative delirium in adult patients who have undergone cardiac surgery when compared to other anesthetics. But obvious heterogeneity are present in the RCTs published in these studies. Future high-quality, large scale, randomized controlled clinical trials are still needed to verify the protective effects of dexmedetomidine against postoperative delirium in sub-population of cardiac surgery patients.

**Abbreviations**

DEX, dexmedetomidine;

NS, normal saline;

CAM, Confusion Assessment Method;

CAM-ICU, CAM for Intensive Care Unit;

RASS, Richmond Agitation Sedation Scale;

CPB, cardiopulmonary bypass;

CABG, coronary artery bypass grafting;

AF, atrial fibrillation;

**Declarations**

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** All data generated or analysed during this study are included in this published article [and its supplementary information files].

**Competing interests:** The authors declare that they have no competing interests

**Funding:** This work was supported by the National Natural Science Foundation of China (82072147) and Shanghai Science and Technology Innovation Project (16411950300). They funded the research for the project.

**Authors’ contributions:**

PL wrote the protocol and the review, searched the studies, quantified the risk of bias, extracted the data, and approve the manuscript before submission;

LL wrote the protocol and the review, searched the studies, quantified the risk of bias, extracted the data, and approve the manuscript before submission;

ZZ helped write the protocol and the review, and approve the manuscript before submission;

JX helped approve the protocol and the manuscript before submission and write the review;

This manuscript was handled by JW and XD.

All authors have read and approved the manuscript.

**Acknowledgements:** Not applicable

**References**

[1] A. Rudiger, H. Begdeda, D. Babic, B. Kruger, B. Seifert, M. Schubert, D.R. Spahn, D. Bettes, Intra-operative events during cardiac surgery are risk factors for the development of delirium in the ICU, Crit Care, 20 (2016) 264.

[2] C. Cropsey, J. Kennedy, J. Han, P. Pandharipande, Cognitive Dysfunction, Delirium, and Stroke in Cardiac Surgery Patients, Semin Cardiothorac Vasc Anesth, 19 (2015) 309-317.

[3] S. Deiner, X. Luo, H.M. Lin, D.I. Sessler, L. Saager, F.E. Sieber, H.B. Lee, M. Sano, G. and the Delirium Writing, C. Jankowski, S.D. Bergese, K. Candiotti, J.H. Flaherty, H. Arora, A. Shander, P. Rock, Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial, JAMA Surg, 152 (2017) e171505.

[4] G. Djaiani, N. Silverton, L. Fedorko, J. Carroll, R. Styra, V. Rao, R. Katzenelson, Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial, Anesthesiology, 124 (2016) 362-368.
[5] F. Ji, Z. Li, H. Nguyen, N. Young, P. Shi, N. Fleming, H. Liu, Perioperative dexmedetomidine improves outcomes of cardiac surgery, Circulation, 127 (2013) 1576-1584.

[6] A. Scicutella, The pharmacotherapeutic management of postoperative delirium: an expert update, Expert Opin Pharmacother, 21 (2020) 905-916.

[7] M. Wu, Y. Liang, Z. Dai, S. Wang, Perioperative dexmedetomidine reduces delirium after cardiac surgery: A meta-analysis of randomized controlled trials, Journal of Clinical Anesthesia, 50 (2018) 33-42.

[8] G. Wang, J. Niu, Z. Li, H. Lv, H. Cai, The efficacy and safety of dexmedetomidine in cardiac surgery patients: A systematic review and meta-analysis, PLoS ONE, 13 (2018).

[9] A. Turan, A. Duncan, S. Leung, N. Karimi, J. Fang, G. Mao, J. Hargrave, M. Gillinov, C. Trombetta, S. Ayad, M. Hassan, A. Feider, K. Howard-Quijano, K. Ruetzler, D.I. Sessler, S. Bergese, G. De Oliveira, H. Honar, A. Niazi, K. Elliott, H. Hamadnalla, P. Chodavarapu, G. Bajracharya, P. Fitzgerald, E. Cuko, Z. Akhtar, C. Lokhade, M.Z. Khan, D. Khoshknabi, Q. Riter, M. Hutcherson, S. Yagar, L. Glosse, P. Saha, S. Raza, Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial, The Lancet, 396 (2020) 177-185.

[10] B. Subramaniam, P. Shankar, S. Shaefi, A. Mueller, B. O’Gara, V. Banner-Goodspeed, J. Gallagher, D. Gasangwa, M. Patxot, S. Packiasabapathy, P. Mathur, M. Eikermann, D. Talmor, E.R. Marcantonio, Effect of Intravenous Acetaminophen vs Placebo Combined with Propofol or Dexmedetomidine on Postoperative Delirium among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial, JAMA - Journal of the American Medical Association, 321 (2019) 686-696.

[11] B. Hutton, G. Salanti, D.M. Caldwell, A. Chaimani, C.H. Schmid, C. Cameron, J.P. Ioannidis, S. Straus, K. Thorlund, J.P. Jansen, C. Mulrow, F. Catala-Lopez, P.C. Gotzsche, K. Dickersin, I. Boutron, D.G. Altman, D. Moher, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Ann Intern Med, 162 (2015) 777-784.

[12] S. Priye, S. Jagannath, D. Singh, S. Shivaprakash, D.P. Reddy, Dexmedetomidine as an adjunct in postoperative analgesia following cardiac surgery: A randomized, double-blind study, Saudi Journal of Anaesthesia, 9 (2015) 353-358.

[13] G. Massoumi, M. Mansouri, S. Khamesipour, Comparison of the incidence and severity of delirium and biochemical factors after coronary artery bypass grafting with dexmedetomidine: A randomized double-blind placebo-controlled clinical trial study, ARYA Atherosclerosis, 15 (2019) 14-21.

[14] X. Li, J. Yang, X.L. Nie, Y. Zhang, X.Y. Li, L.H. Li, D.X. Wang, D. Ma, Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial, PLoS ONE, 12 (2017).

[15] O.O. Balkanay, D. Goksedef, S.N. Omeroglu, G. Ipek, The dose-related effects of Dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: A randomized, triple-blind, placebo-controlled study, Interactive Cardiovascular and Thoracic Surgery, 20 (2015) 209-214.

[16] C. Shi, J. Jin, L. Qiao, T. Li, J. Ma, Z. Ma, Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: A double-blind, multi-center, randomized study, Clinical Interventions in Aging, 14 (2019) 571-575.

[17] X. Liu, K. Zhang, W. Wang, G. Xie, B. Cheng, Y. Wang, Y. Hu, X. Fang, Dexmedetomidine Versus Propofol Sedation Improves Sublingual Microcirculation After Cardiac Surgery: A Randomized Controlled Trial, Journal of Cardiothoracic and Vascular Anesthesia, 30 (2016) 1509-1515.

[18] S.M. Corbett, J.A. Rebuck, C.M. Greene, P.W. Callas, B.W. Neale, M.A. Healey, B.J. Leavitt, Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation, Critical Care Medicine, 33 (2005) 940-945.

[19] J.B. Park, S.H. Bang, H.K. Chee, J.S. Kim, S.A. Lee, J.K. Shin, Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass, Korean J Thorac Cardiovasc Surg, 47 (2014) 249-254.

[20] H. Shokri, I. Ali, A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary artery bypass grafting, Journal of Clinical Anesthesia, 61 (2020).

[21] Y. Shehabi, Prevalence of Delirium with Dexmedetomidine Compared with Morphine Based Therapy after Cardiac Surgery: A Randomized Controlled Trial, Journal of Cardiothoracic and Vascular Anesthesia, 30 (2016) 1509-1515.

[22] G. Wang, J. Niu, Z. Li, H. Lv, H. Cai, The efficacy and safety of dexmedetomidine in cardiac surgery patients: A systematic review and meta-analysis, PLoS ONE, 13 (2018).

[23] T.M.A. Azeem, N.E. Yosif, A.M. Alansary, I.M. Esmat, A.K. Mohamed, Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; A randomized, double-blinded clinical trial, Saudi Journal of Anaesthesia, 12 (2018) 190-197.

[24] X. Duan, M. Coburn, R. Rossaint, R.D. Sanders, J.V. Waesberghe, A. Kowark, Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials, British Journal of Anaesthesia, 121 (2018) 384-397.
[25] Q.H. Shen, H.F. Li, X.Y. Zhou, X.Z. Yuan, Dexmedetomidine in the prevention of postoperative delirium in elderly patients following non-cardiac surgery: A systematic review and meta-analysis, Clinical and Experimental Pharmacology and Physiology, 47 (2020) 1333-1341.

[26] A. Maheshwari, P.J. McCormick, D.J. Sessler, D.L. Reich, J. You, E.J. Mascha, J.G. Castillo, M.A. Levin, A.E. Duncan, Prolonged concurrent hypotension and low bispectral index (‘double low’) are associated with mortality, serious complications, and prolonged hospitalization after cardiac surgery, Br J Anaesth, 119 (2017) 40-49.

[27] E.M. Wesselink, T.H. Kappen, W.A. van Klei, J.M. Dieleman, D. van Dijk, A.J. Slooter, Intraoperative hypotension and delirium after on-pump cardiac surgery, Br J Anaesth, 115 (2015) 427-433.

[28] V.S. Eckle, C. Grasshoff, Do we need a manual jugular venous compression manoeuvre?, Br J Anaesth, 116 (2016) 885-886.

[29] D. Hori, C. Brown, M. Ono, T. Rappold, F. Sieber, A. Gottschalk, K.J. Neufeld, R. Gottesman, H. Adachi, C.W. Hogue, Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium, Br J Anaesth, 113 (2014) 1009-1017.

[30] D. Hori, L. Max, A. Laflam, C. Brown, K.J. Neufeld, H. Adachi, C. Sciortino, J.V. Conte, D.E. Cameron, C.W. Hogue, Jr., K. Mandal, Blood Pressure Deviations From Optimal Mean Arterial Pressure During Cardiac Surgery Measured With a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study, J Cardiothorac Vasc Anesth, 30 (2016) 606-612.

[31] G. Sanson, Y. Khlopenyuk, S. Milocco, M. Sartori, L. Dreas, A. Fabiani, Delirium after cardiac surgery. Incidence, phenotypes, predisposing and precipitating risk factors, and effects, Heart Lung, 47 (2018) 408-417.

[32] H. Tan, J. Bi, Y. Wang, J. Zhang, Z. Zuo, Transfusion of Old RBCs Induces Neuroinflammation and Cognitive Impairment, Crit Care Med, 43 (2015) e276-286.

[33] C.R. Barends, A. Absalom, B. van Minnen, A. Vissink, A. Visser, Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety, PLoS One, 12 (2017) e0169525.

[34] D.L. Herr, S.T.J. Sum-Ping, M. England, ICU Sedation After Coronary Artery Bypass Graft Surgery: Dexmedetomidine-Based Versus Propofol-Based Sedation Regimens, Journal of Cardiothoracic and Vascular Anesthesia, 17 (2003) 576-584.