Does dexmedetomidine reduce the risk of acute kidney injury after cardiac surgery: a meta-analysis of randomized controlled trials

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Abstract

OBJECTIVE: Acute kidney injury (AKI) is a common complication after cardiac surgery, and there is no pharmacologic prophylaxis of AKI. Some animal and clinical studies showed the renoprotection effect of dexmedetomidine (DEX) on AKI, but data from other trials came to the opposite conclusion following cardiac surgery. **METHODS**: We searched databases including EMBASE, PubMed, and Cochrane CENTRAL for randomized controlled trials (RCTs) focused on DEX for AKI in adult patients after cardiac surgery. The primary outcome was incidence of AKI. Secondary outcomes were mechanical ventilation (MV) duration, intensive care unit (ICU) length of stay (LOS), hospital LOS and mortality. **RESULTS**: Fifteen trials enrolling 2907 study patients were collected in the meta-analyses. Compared with controls, DEX reduced the incidence of postoperative AKI [odds ratio (OR), 0.66; 95%confidence interval (CI), 0.48-0.91; P=0.01], and there was no significant difference between groups in postoperative mortality (OR, 0.63; 95%CI, 0.32-1.26; P=0.19), MV duration [weighted mean difference(WMD), -0.44; 95%CI, -1.50-0.63; P=0.42], ICU LOS (WMD, -1.19; 95%CI, -2.89-0.51; P=0.17) and hospital LOS (WMD, -0.31; 95%CI, -0.76-0.15; P=0.19). **CONCLUSIONS**: Perioperative DEX use reduced the incidence of postoperative AKI in adult patients undergoing cardiac surgery. No significant decrease existed in mortality, MV duration, ICU LOS and hospital LOS owing to the DEX administration.

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Statement

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RESULTS : Fifteen trials enrolling 2907 study patients were collected in the meta-analyses. Compared with controls, DEX reduced the incidence of postoperative AKI [odds ratio (OR), 0.66; 95%confidence interval (CI), 0.48-0.91; P=0.01], and there was no significant difference between groups in postoperative mortality (OR, 0.63; 95%CI, 0.32-1.26; P=0.19), MV duration [weighted mean difference(WMD), -0.44; 95%CI, -1.50-0.63; P=0.42], ICU LOS (WMD, -1.19; 95%CI, -2.89-0.51; P=0.17) and hospital LOS (WMD, -0.31; 95%CI, -0.76-0.15; P=0.19).

CONCLUSIONS : Perioperative DEX use reduced the incidence of postoperative AKI in adult patients undergoing cardiac surgery. No significant decrease existed in mortality, MV duration, ICU LOS and hospital LOS owing to the DEX administration.

Keywords : Dexmedetomidine; Acute kidney injury; Cardiac surgery; Meta-analysis.

1.Background

Acute kidney injury (AKI) is a recognized complication following cardiac surgery with a reported incidence between 5% and 42%[1]. Postoperative AKI results in poor outcomes, prolonged hospital length of stay (LOS), increased hospital costs and mortality[2]. The mechanism of AKI after cardiac surgery is tightly associated with the hemodynamic instability and sympathetic activity during cardiopulmonary bypass (CPB)[3-5]. Although numerous trials attempted to identify strategies to prevent AKI, the incidence is still around 40% and no definite strategy exists yet[6-10].

Dexmedetomidine (DEX) is a highly selective α2 adrenoreceptor agonist and has been widely used for sedation during cardiac surgery. DEX differs from other sedatives by the properties of anti-inflammatory and sympatholytics[11, 12]. These properties suggest that DEX might reduce the incidence of postoperative AKI. Preclinical studies indicated the renoprotective effect of DEX in various animal models[13-15]. Several single-center randomized controlled trials (RCTs) have also addressed this question and the results are controversial[16-19]. Previous meta-analyses had evaluated the effect of DEX in cardiac surgery and showed a reduced risk of postoperative AKI[20-22]. However, the studies were limited by high heterogeneity and relatively small sample size. Moreover, some strengthened studies focused on this issue were published in recent years[23, 24]. Therefore, we conducted a new meta-analysis to evaluate the effect of perioperative DEX on the incidence for AKI after cardiac surgery.

2.Methods

2.1 Search Strategy and Study Criteria

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[25]and three electronic databases including MEDLINE (through PubMed), Embase (through OVID) and Cochrane Library were searched to identify relevant studies. The search strategy for PubMed was performed using the keywords "dexmedetomidine," "cardiac surgery," "heart surgery," "kidney," and "renal". Various combinations of key words and different search strategies were developed for another two databases. The search encompassed the period January 1997 until the July 2021. All eligible studies met the following conditions: (1) randomized controlled trials only, and as an original article, (2) studies published in English, (3) adult patients undergoing cardiac surgery with or without cardiopulmonary bypass; (3) intervention: DEX; (4) comparison: placebo or control (other therapy); (5) outcome measure: the incidence of postoperative AKI. Exclusion criteria were as follows: retrospective study, observational study, conference abstracts, expert opinion, review articles, case reports, abstracts, editorials, and letters to the editor, animal studies, studies involving pediatric population, and studies lacked clinical outcome data and failure to contact the authors. Furthermore, the reference of relevant studies was also assessed.

2.2 Literature Review and Data Extraction

The literature review and data extraction were independently completed by 2 investigators. In the case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion to reach consensus. Quality assessment was completed using the Cochrane risk of bias tool: randomization, allocation concealment, blinding, withdrawals and dropouts, and intention-to-treat analysis. Data extraction included characteristics of included studies and patients.

2.3 Postoperative Outcomes

The primary end point was incidence of AKI (defined as RIFLE,AKIN ,KDIGO or need dialysis within 7 days after cardiac surgery). Secondary outcomes included mortality, mechanical ventilation (MV) duration, ICU LOS, and hospital LOS.

2.4 Statistical Analysis

For dichotomous outcomes (reported with incidence), we calculated the odds ratio (OR) with 95% confidence interval (CI). For continuous outcomes (reported as mean±standard deviation, median and interquartile range, or median and range), we calculated mean differences for each study according to the statistical method of Hozo et al[26] and used weights to pool the estimate (weighted mean difference, WMD) with 95% CI. Random-effects models were used to analyze the data in light of the heterogeneity. Heterogeneity was assessed with the inconsistency statistic (I^2). Publication bias was assessed by Begg's test, Egger's test and Macaskill test. Meta-regression and subgroup analysis were conducted to explore the potential sources of significant heterogeneity. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates. $P<0.05$ (2 sided) was considered to be statistically significant for hypothesis testing. All statistical analyses were performed in REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 15.0; StataCorp LP).

3.Results

3.1 Study Characteristics

Figure 1 showed flow chart for the study screening and selection process in this meta-analysis. Fifteen trials with sixteen group of dataultimately met our criteria[16-19, 23, 24, 27-35]. Two studies were for coronary artery bypass grafting, nine were for combined cardiac surgery, two for valve replacement surgery and two was for aortic vascular surgery. Nine trials used placebo as control, whereas four used propofol, one used morphine or remifentanil. DEX was continuously infused at a rate of approximately 0.2 to 0.8ug/kg/h for 24 hours after a loading dose (0.4-1ug/kg) in six studies or infused at a rate of approximately 0.04 to 1.5ug/kg/h without a loading dose in nine.

For postoperative outcomes, AKI incidence was reported in thirteen trials; need for dialysis, in two; mortality,

in seven; mechanical ventilation duration, in twelve; ICU LOS, in thirteen; and hospital LOS, in ten.

Study design and patient characteristics are summarized in Tables 1 and 2. The quality assessment is listed in Table 3.

3.2 Effect of DEX on Incidence of AKI, and Mortality

The outcome of AKI was reported in 2907 study participants, and the overall incidence was 7.95% (DEX group, 6.52%; control group, 9.37%). The postoperative incidence of AKI was significantly reduced by DEX (fifteen studies; OR, 0.66; 95% CI, 0.48-0.91; P=0.01; I^2=6%; Figure 2). There was no evidence of publication bias (Begg's test P = 0.96; Egger's test P = 0.55).

Subgroup analyses revealed similar trends to those of postoperative AKI outcome based on different characteristics such as age ([?]62.5 versus <62.5 years), male proportion ([?]62% versus <62%), diabetes proportion ([?]25% versus <25%), hypertension proportion ([?]25% versus <25%), Previous myocardial infarction (MI) proportion ([?]15% versus <15%), left ventricular ejection fraction (LVEF) ([?]60% versus <60%), cardiopulmonary bypass (CPB) duration ([?]100 versus < 100 minutes), β-blocker ([?]50% versus <50%), Statin ([?]65% versus <65%),loading dose (use or not), type of control (placebo versus others), administration timing (pre/intraoperative versus postoperative) and surgery type (combined surgery versus others) (Table 4).

Meta-regression analyses performed for the potential sources of significant heterogeneity were listed in Table 5, and there were no significant differences for postoperative AKI in all the subgroups.

Sensitivity analyses excluding each included study at a time revealed that all the studies were consistent with the direction and size of the overall AKI-reducing effect of DEX (P for all < 0.05) except Cho.

The outcome of mortality was reported in 1883 study participants, and the overall incidence was 1.86% (DEX group, 1.38%; control group, 2.34%). There was no significantly difference between DEX with the risk of mortality (Seven studies; OR, 0.63; 95% CI, 0.32-1.26; P=0.19; I^2=0%; Figure 4).

3.3 Effect of DEX on MV Duration, ICU LOS and Hospital LOS.

Postoperative MV duration were reported in twelve studies, and no statistically significant reduction by DEX was found (eleven studies; WMD, -0.44; 95%CI, -1.50- 0.63; P=0.42; I^2=73%; Figure 5). There was no significant difference in ICU LOS (thirteen studies; WMD, -1.19; 95%CI, -2.89-0.51; P=0.17; I^2=74%; Figure 6), as well as the hospital LOS (ten studies; WMD, -0.31; 95%CI, -0.76-0.15; P=0.19; I^2=76%; Figure 7).

4. Discussion

In this meta-analysis of fifteen RCTs involving 2907 adult patients undergoing cardiac surgery, we found that perioperative DEX use was associated with a decrease in postoperative AKI. However, postoperative parameters including MV duration, ICU, hospital LOS and mortality appeared no significant reduction as a result of the DEX.

AKI is common after cardiac surgery and small increases in postoperative serum creatinine levels have been reported to be related with worse outcome, even the renal function returns to normal ultimately[36, 37]. For this reason, pharmacologic or other prophylaxis to lower the AKI after cardiac surgery is an important research area to clinicians.

DEX was thought to have a profound renal protection by stabilizing the sympathetic system, exerting anti-inflammatory effects and attenuating ischemia/reperfusion (I/R) injury in vivo and vitro studies[38-42]. The present meta-analysis combining all these positive and negative clinical studies showed that perioperative DEX use reduced the incidence of AKI after cardiac surgery. There were some meta-analyses focused on this issue. However, a meta-analysis performed by Peng[20], which included nine RCTs with a total of 1308 patients, showed a low heterogeneity (I^2= 30%). Another meta-analyses by Liu[21] included ten RCTs with a total of 1575 patients showed only eight group of data from seven studies about the main outcome. Our

study with almost two times larger sample size collected some high-quality research published in recent years and provided more convinced conclusion.

Our analysis has several limitations. Firstly, the definition of AKI varied in the included trials, which may have introduced bias. Secondly, some individual patient data including the existed renal impairment before surgery were not reported in the enrolled studies. Thirdly, sample size is relatively low, so future large clinical studies were needed.

In summary, our meta-analysis indicated that perioperative DEX use reduced the postoperative AKI in patients receiving cardiac surgery. However, DEX use is not associated with MV duration, ICU LOS, hospital LOS and mortality. Future trials are needed to be much larger to verify the current findings.

Figure legends

Figure 1: Flow diagram of studies included into meta-analyses

Figure 2: Quality Assessment of studies included into meta-analyses

Figure 3: DEX reduced the incidence of AKI

Figures 4: Forest plot for postoperative mortality

Figures 5: Forest plot for MV duration

Figures 6: Forest plot for ICU LOS

Figures 7: Forest plot for hospital LOS

Table legends

Table 1: Summarized Study Design of Included Randomized Trials

Table 2: Summarized patient characteristic of the included randomized trials

Table 3: Summarized Quality Assessment of Included Randomized Trials

Table 4: Subgroup analyses for the potential sources of heterogeneity

Table 5: Meta-regression for the potential sources of heterogeneity

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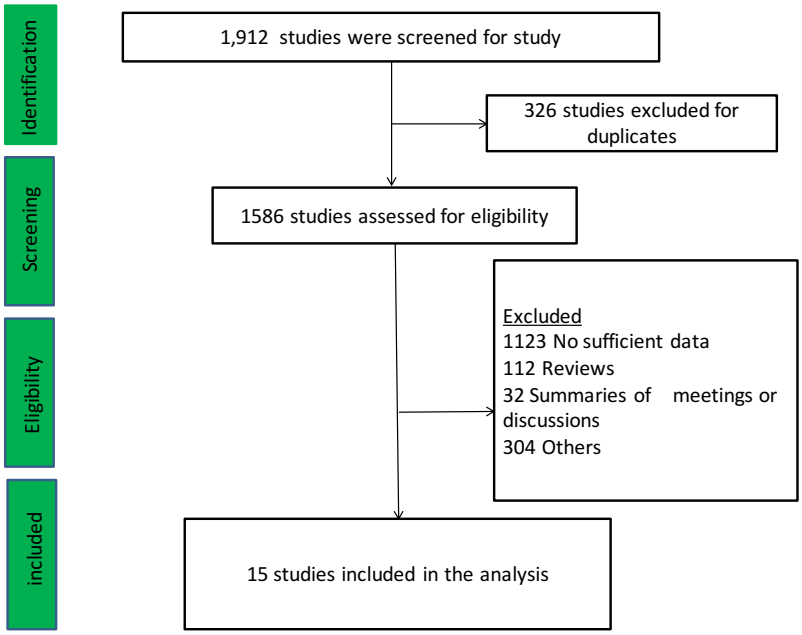
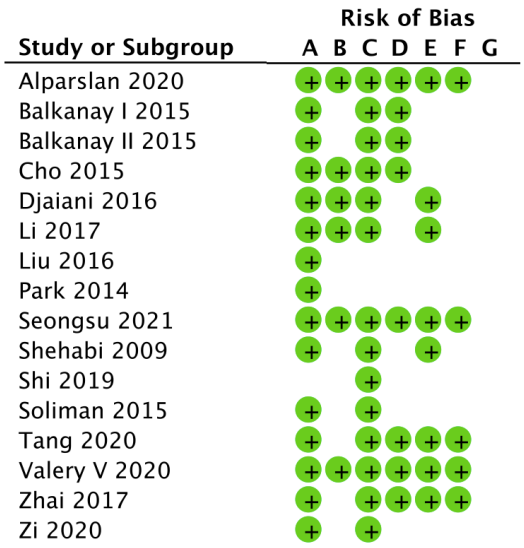
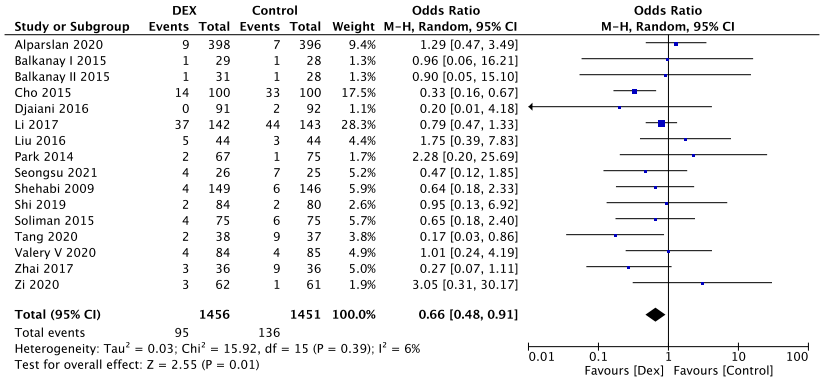
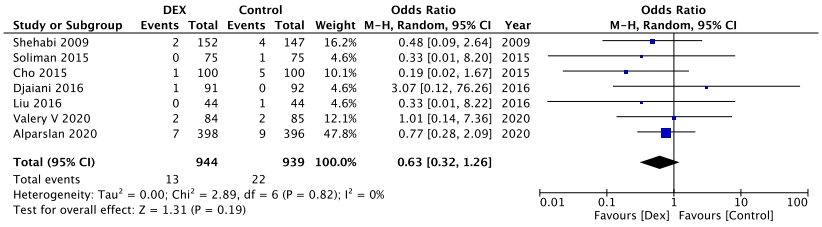
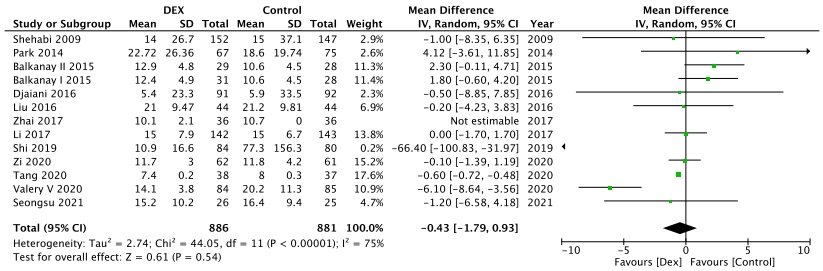


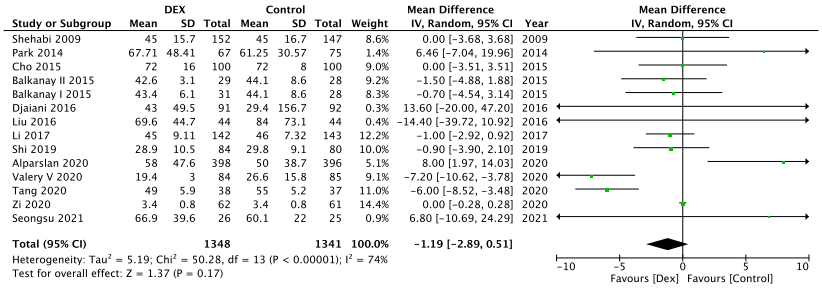


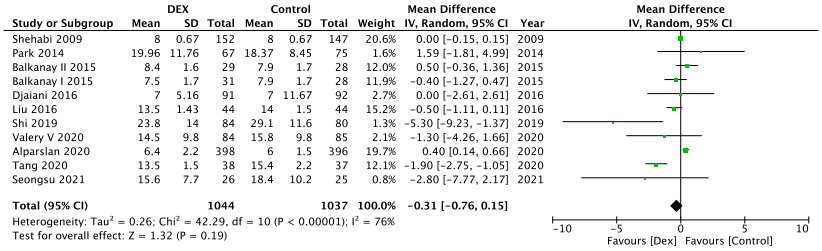
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias











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