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Effect of Dexmedetomidine on Cardiac Surgery-Associated Acute Kidney Injury: A Meta-Analysis With Trial Sequential Analysis of Randomized Controlled Trials

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Objective: Cardiac surgery-associated acute kidney injury (CS-AKI) is associated with high mortality rates. This study aimed to determine the effects of perioperative dexmedetomidine (DEX) administration on CS-AKI in adult patients.

Design: A meta-analysis with trial sequential analysis of randomized controlled trials.

Setting: PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure databases were searched up to March 11, 2019 for relevant articles. The study protocol was registered at the International Prospective Register of Systematic Reviews (registration number: CRD42019128139).

Participants: Adult patients undergoing cardiac surgery.

Interventions: Dexmedetomidine compared with controls.

Measurements and Main Results: Nine randomized controlled trials with a total of 1,308 patients were included. Use of DEX significantly reduced the incidence of CS-AKI (risk ratio = 0.60, 95% confidence interval = 0.41-0.87, \( p = 0.008, I^2 = 30\% \)), without significant publication bias. The trial sequential analysis result suggested that there was enough evidence for this outcome. Sensitivity analysis confirmed the robustness of the result. The improvement of CS-AKI was primarily significant in preoperative and/or intraoperative administration of DEX with or without postoperative continuation, patients with age \( \geq 60 \) years, and studies with low risk of bias. The subgroup analysis did not show statistical differences. Dexmedetomidine use also was associated with less prolonged ventilation and lower incidences of pulmonary complications and delirium postoperatively. The level of evidence was high for the incidence of CS-AKI on the Grading of Recommendations Assessment, Development and Evaluation profile.

Conclusion: Perioperative DEX administration provided protective effects against CS-AKI, especially when initiated before and during surgery in elderly patients.

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Key Words: dexmedetomidine; cardiac surgery; acute kidney injury; meta-analysis; trial sequential analysis
hemodynamic disturbance, inflammation, and especially exposure of blood to the cardiopulmonary bypass (CPB) circuit. However, there are no validated strategies for preventing CS-AKI.

Dexmedetomidine (DEX), a highly selective α2-adrenergic agonist, produces sedative, analgesic, sympatholytic, and anti-inflammatory effects for surgical patients. Studies suggest that DEX may provide renal protection for patients undergoing cardiac surgery. In the authors’ previous retrospective cohort study, post-bypass use of DEX was associated with a lower incidence of CS-AKI, especially in patients with normal kidney function or mild chronic kidney disease before surgery. To date, there are 2 meta-analyses that evaluated the effects of DEX on CS-AKI. However, 1 meta-analysis included only 3 randomized controlled trials (RCTs) as well as 4 cohort studies, leading to a lower level of evidence for the outcomes. The other meta-analysis failed to include the most recent RCT, and did not assess the reliability or the level of evidence. Thus, whether DEX could reduce CS-AKI in adult patients needs further investigation.

This meta-analysis aimed to determine the protective effects of DEX against CS-AKI based on the evidence of all published RCTs. The primary outcome measure of this study was the incidence of postoperative CS-AKI. Furthermore, trial sequential analysis (TSA) was conducted to evaluate the reliability of the primary outcome, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was employed to assess the level of evidence.

Methods

For this systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the recommendations of Cochrane Collaboration were followed. The review protocol was specified in advance and registered at the International Prospective Register of Systematic Reviews (registration number CRD42019128139; available at: https://www.crd.york.ac.uk/PROSPERO). The PRISMA checklist is shown in Supplementary Table 1.

Literature Search

Three review authors independently searched PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure databases from inception to March 11, 2019. Medical subject headings terms combined with text words were applied, without language or journal restrictions. The search strategies for PubMed, EMBASE, and Cochrane Library are detailed in Supplementary Table 2. The reference lists from relevant publications also were checked manually for additional studies. All search results were imported into EndNote software (version X7.8, Thomson Reuters, NY).

Trial Selection

Three review authors independently screened the search results to identify relevant studies. The eligibility criteria were defined prior to the literature search. The inclusion criteria were (1) RCT only, (2) adult patients undergoing cardiac surgery, (3) perioperative use of DEX compared to a control group with saline or other sedatives/analgesics, and (4) outcomes on postoperative AKI. The exclusion criteria were (1) study types other than RCT, (2) pediatric patients, (3) no specific outcomes, or (4) report on the use of dialysis/renal replacement therapy other than AKI incidence. Any discrepancy over trial selection was resolved by re-evaluation of the full-text study and a consensus with the other review authors.

Data Extraction

Three review authors independently extracted the following data: first author, year of publication, region, comparative groups, sample size, age, surgical procedure, time of intervention, AKI definition, and main outcomes reported. The corresponding authors of the included studies were contacted if data were incomplete. Any discrepancy at this step was resolved by re-examination of the data and a consensus with the other review authors.

Outcome Measures

The incidence of CS-AKI was designated as the primary outcome. The AKI cases included in this meta-analysis were based on the AKI criteria used in each original study. For the definition of AKI, Risk—Injury—Failure—Loss—End-stage renal disease, Acute Kidney Injury Network, and Kidney Disease Improving Global Outcomes criteria are shown in Supplementary Table 3.

The secondary outcome measures included urine output, time to extubation, prolonged ventilation, pulmonary complications, delirium, atrial fibrillation, wound infection, reoperation, postoperative hypotension, postoperative bradycardia, length of intensive care unit (ICU) stay, length of hospital stay, and in-hospital mortality.

Quality Assessment

Three review authors independently assessed the risk of bias for the included studies using the Cochrane Collaboration tool and the quality of evidence for main outcomes using the GRADE approach. Any discrepancy over quality assessment was resolved by re-evaluation of the studies/outcomes and a consensus with the other review authors.

Using the Cochrane’s tool, each RCT was evaluated in several domains including selection bias (random sequence generation and allocation concealment), performance and detection bias (blinding of participants, personnel, and outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. First, a judgment of high, low, or unclear risk of bias was made for each domain of a study. Next, the study was rated to be at a low risk of bias (low risk for all domains), a high risk of bias (high risk for 1 or more domains), or otherwise an unclear risk of bias. Using the GRADE methodology, each outcome was rated as high,
moderate, low, or very low quality of evidence based on 5
domains including risk of bias, inconsistency, indirectness,
imprecision, and other considerations.

Meta-Analysis

One review author performed the meta-analyses using Rev-
Man software version 5.3 (Cochrane Collaboration, Copen-
Hagen, Denmark), and another 2 authors checked the pooled
results. The risk ratio (RR) and its 95% confidence interval (CI)
were calculated for dichotomous outcomes, while the weighted
mean difference or standard mean difference were employed
for continuous outcomes. Data were combined only when 3 or
more trial results were available to be included for an outcome.
Considering the clinical heterogeneity among the included
studies, a random-effects model was used for all outcome
analyses.13,17 Heterogeneity was evaluated using the I² statistic,
and I² > 50% indicated significant heterogeneity.18 Publication
bias was assessed using Egger’s linear regression test and Begg’s
rank correlation test using STATA software version 14.0 (Stata
Corp, College Station, TX).19,20 In addition, Begg’s funnel plot
was generated for visualization. A p value < 0.05 denotes a sta-
tistical significance.

Trial Sequential Analysis

In a meta-analysis, repetitive tests of accumulating data
increase the risk of type I error, which is known as a false-positi-
ve finding.21,22 To deal with this issue, the TSA approach of
monitoring boundaries is used to help determine whether the
current evidence is sufficient and conclusive. In a TSA dia-
agram, a cumulative Z curve that crosses the trial sequential
monitoring boundary or the futility boundary indicates a suffi-
cient level of evidence for a conclusion and no need for further
studies; otherwise, if the Z curve does not cross any boundary
and the required information size (RIS) is not achieved, the
current evidence is insufficient.17,21,22

One review author examined the reliability of the primary
outcome using TSA viewer software version 0.9.5.5 beta
(Copenhagen Trial Unit, Centre for Clinical Intervention
Research, Rigshospitalet, Copenhagen), and another 2 authors
checked the results. The RIS of 1,835 was calculated by 2-
sided testing with \( \alpha = 0.05 \), power = 80%, and an anticipated
33% decrease in the incidence of AKI for the DEX group ver-
sus the control group.

Sensitivity and Subgroup Analyses

One review author further evaluated the robustness and
potential sources of heterogeneity of the primary outcome
using sensitivity and subgroup analyses. The results were
checked by another 2 authors. In the sensitivity analysis, the
effect of a single study on the overall estimated outcome was
evaluated by omitting 1 study at a time.17 In the subgroup anal-
yses, the primary outcome was stratified by time of interven-
tion (preoperative and/or intraoperative administration of DEX
with or without postoperative continuation v postoperative
administration only), age (≥60 years v < 60 years), and quality
of studies (low-risk studies v high/unclear risk studies).

Results

Literature Search

A total of 245 publications were identified initially, of which
45 duplicates were removed by EndNote. After title and abstract
screening, 19 full-text articles were reviewed. Of these, 10 were
excluded owing to lack of specific outcomes on AKI. A final
total of 9 RCTs were included in this meta-analysis.6-9,23-27 The
PRISMA flow diagram is presented in Figure 1.

Study Characteristics

Details of included RCTs, including country, intervention
arms, sample size, type of surgery, time of intervention, AKI
definition, and outcome measures, are summarized in Table 1.
A total of 1,308 patients (675 patients in the DEX group and
633 patients in the control group) were included. All patients
underwent nonemergency cardiac surgeries, primary elective
coronary artery bypass graft, and/or valve replacement proce-
dures on CPB. In 6 studies, DEX was administered before/after
anesthesia induction and continued postoperatively for up to
24 hours.6-8,23,26,27 In the other 3 studies, DEX was used only
for postoperative sedation in the ICU.9,24,25 For the AKI crite-
ria, Risk—Injury—Failure—Loss—End-stage renal disease was
used in 3 studies,7,9 Acute Kidney Injury Network in 2 studies,6,24
Kidney Disease Improving Global Outcomes in 2 studies,23,27
serum creatinine > 2.0 times baseline in 1 study,25 and serum
creatinine > 115 μmol/L in 1 study.26

Risk of Bias Assessment

The results of risk assessment are shown in Figure 2. All
included studies were randomized trials. Five trials had low
risk of biases in all domains,6-8,23,25 and 4 had unclear risk for
selection bias, attrition bias, and reporting bias.6,9,24,26,27 There
was no trial at high risk of bias. In addition, no risk of conflict
of interest among the authors was reported.

Primary Outcome

Main outcomes are listed in Table 2. The use of DEX was
associated with a significantly lower incidence of CS-AKI com-
pared to the control group (10.9% v 18.3%; RR = 0.60, 95%
CI = 0.41-0.87, p = 0.008, I² = 30%; Fig 3, A). Based on the
TSA result, although the RIS was not reached, the cumulative
Z-curve (blue) crossed the trial sequential monitoring boundary,
suggesting enough evidence for this outcome (Fig 3, B).
To explore the robustness of this finding, sensitivity analysis
was performed by omitting 1 study at a time. The results
showed that the estimated benefits of DEX on the AKI inci-
dence ranged from RR = 0.48 (95% CI = 0.33-0.71) by omit-
ting Li (2017) to RR = 0.67 (95% CI = 0.45-1.00) by omitting
Cho (2016), indicating that no single study significantly
influenced the overall result (Fig 4, A). No significant publication bias was detected with Egger’s test (p = 0.892) or Begg’s funnel plot (p = 0.174; Fig 4, B).

In addition, subgroup analyses showed that the current finding was mainly evident in preoperative and/or intraoperative administration with or without postoperative continuation of DEX (RR = 0.52, 95% CI = 0.32-0.84, p = 0.007; Fig 5, A), in patients with age ≥60 years (RR = 0.65, 95% CI = 0.43-1.00, p = 0.05; Fig 5, B), and in studies with low risk of bias (RR = 0.59, 95% CI = 0.36-0.94, p = 0.03; Fig 5, C). However, the data did not provide evidence to support the significance of any subgroup differences: preoperative and/or intraoperative administration of DEX with or without postoperative continuation versus postoperative administration only (p = 0.20), patients with age ≥60 years versus <60 years (p = 0.62), and low-risk studies versus high/unclear risk studies (p = 0.87).

**Secondary Outcomes**

The use of DEX also was associated with less prolonged ventilation (RR = 0.36, 95% CI = 0.20-0.65, p = 0.0007; Supplementary Fig 1, A) and lower incidences of pulmonary complications (RR = 0.55, 95% CI = 0.31-0.96, p = 0.04; Supplementary Fig 1, B) and delirium (RR = 0.54, 95% CI = 0.32-0.90, p = 0.02; Supplementary Fig 1, C). There were no significant differences in other postoperative complications, urine output, length of ICU stay (Supplementary Fig 2, A), length of hospital stay (Supplementary Fig 2, B), or in-hospital mortality (Supplementary Fig 2, C).

Of note, the incidence of postoperative hypotension (RR = 0.89, 95% CI = 0.36-2.19, p = 0.79; Supplementary Fig 3, A) and bradycardia (RR = 1.44, 95% CI = 0.31-6.71, p = 0.64; Supplementary Fig 3, B) were similar between the
DEX and control groups. Besides, these hemodynamic adverse events were well tolerated in all patients, without the need for more vasopressors or discontinuation of DEX administration.

**Discussion**

This meta-analysis demonstrates that perioperative DEX administration reduced CS-AKI in adult patients. The reliability of this finding was confirmed by TSA. Subgroup analyses showed that protection against CS-AKI provided by DEX was mainly significant in preoperative and/or intraoperative administration with or without postoperative continuation of DEX, in patients with age ≥60 years, and in studies with low risk of bias. DEX use also was associated with less prolonged ventilation and lower incidences of pulmonary complications and delirium. No significant differences were found in other postoperative complications, urine output, length of ICU stay, hospital and ICU stay, mortality.

**Table 1**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country</th>
<th>Group (Number of Patients)</th>
<th>Age (y)</th>
<th>Surgery</th>
<th>Time of Intervention</th>
<th>AKI Definition</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balkanay et al.,9 2015</td>
<td>Turkey</td>
<td>1. DEX &lt;8 μg/kg (31)</td>
<td>60</td>
<td>On-pump CABG</td>
<td>Postoperative sedation for 24 h</td>
<td>RIFLE</td>
<td>AKI, urine output, time to extubation, delirium, atrial fibrillation, reoperation, hypotension, bradycardia, hospital and ICU stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. DEX ≥8 μg/kg (29)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3. Saline (28)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cho et al.,1 2016</td>
<td>Korea</td>
<td>1. DEX 0.4 μg/kg/h (100)</td>
<td>64</td>
<td>Cardiac surgery with CPB</td>
<td>After induction, until postoperative 24 h</td>
<td>AKIN</td>
<td>AKI, urine output, prolonged ventilation, pulmonary complication, infection, reoperation, ICU stay, mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Saline (100)</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leino et al.,6 2011</td>
<td>Finland</td>
<td>1. DEX 0.6 ng/mL (35)</td>
<td>59</td>
<td>On-pump CABG</td>
<td>After induction, until postoperative 4 h</td>
<td>RIFLE</td>
<td>AKI, time to extubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Saline (31)</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al.,23 2017</td>
<td>China</td>
<td>1. DEX 0.1-0.6 μg/kg/h</td>
<td>66</td>
<td>CABG and/or valve replacement</td>
<td>Before induction, until the end of ventilation</td>
<td>KDIGO</td>
<td>AKI, prolonged ventilation, infection, delirium, time to extubation, pulmonary complication, hypotension, bradycardia, ICU stay, mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(143)</td>
<td>67</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2. Saline (142)</td>
<td></td>
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</tr>
<tr>
<td>Liu et al.,23 2016</td>
<td>China</td>
<td>1. DEX 0.2-1.5 μg/kg/h</td>
<td>53</td>
<td>Cardiac surgery with CPB</td>
<td>Postoperative sedation until extubation</td>
<td>AKIN</td>
<td>AKI, prolonged ventilation, time to extubation, delirium, atrial fibrillation, hospital and ICU stay, mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(44)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>2. Propofol 0.3-3 mg/kg/h (44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Shehabi et al.,24 2009</td>
<td>Australia</td>
<td>1. DEX 0.1-0.7 μg/kg/h</td>
<td>71</td>
<td>Cardiac surgery with CPB</td>
<td>Postoperative sedation until chest drain removal</td>
<td>sCr &gt;2.0 times baseline</td>
<td>AKI, time to extubation, infection, delirium, atrial fibrillation, reoperation, hypotension, bradycardia, hospital and ICU stay, mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(152)</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2. Morphine 10-70 μg/kg</td>
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<td></td>
<td></td>
<td>(kg/147)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Soliman et al.,25 2016</td>
<td>Egypt</td>
<td>1. DEX 1 μg/kg + 0.3 μg/kg/h (75)</td>
<td>58</td>
<td>Aortic vascular surgery</td>
<td>Before induction, until the end of surgery</td>
<td>sCr &gt;115 μmol/L</td>
<td>AKI, pulmonary complication, hypotension, bradycardia, mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(57)</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al.,26 2018</td>
<td>China</td>
<td>1. DEX 0.4-0.8 μg/kg/h</td>
<td>48</td>
<td>Valve replacement with CBP</td>
<td>Before induction, until the end of surgery</td>
<td>KDIGO</td>
<td>AKI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(30)</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Saline (30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhai et al.,7 2017</td>
<td>China</td>
<td>1. DEX 0.6 μg/kg + 0.2 μg/kg/h (36)</td>
<td>45</td>
<td>Valve replacement with CBP</td>
<td>Before induction, until the end of surgery</td>
<td>RIFLE</td>
<td>AKI, urine output, time to extubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(36)</td>
<td>47</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; DEX, dexmedetomidine; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk—Injury—Failure—Loss—End-stage renal disease; sCr, serum creatinine.
Table 2
Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>DEX vs Control (n)</th>
<th>SMD, MD, or RR (95% CI)</th>
<th>p Value</th>
<th>( I^2 (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative AKI</td>
<td>671 vs 633</td>
<td>RR = 0.60 (0.41-0.87)</td>
<td>.008*</td>
<td>30</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>286 vs 287</td>
<td>RR = 0.36 (0.20-0.65)</td>
<td>.0007*</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>317 vs 318</td>
<td>RR = 0.55 (0.31-0.96)</td>
<td>.04*</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>398 vs 362</td>
<td>RR = 0.54 (0.32-0.90)</td>
<td>.02*</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>256 vs 219</td>
<td>RR = 0.53 (0.26-1.09)</td>
<td>.08</td>
<td>58</td>
</tr>
<tr>
<td>Wound infection</td>
<td>394 vs 390</td>
<td>RR = 1.01 (0.36-2.80)</td>
<td>.99</td>
<td>46</td>
</tr>
<tr>
<td>Reoperation</td>
<td>312 vs 275</td>
<td>RR = 0.75 (0.34-1.62)</td>
<td>.46</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative hypotension</td>
<td>354 vs 318</td>
<td>RR = 0.89 (0.36-2.19)</td>
<td>.79</td>
<td>84</td>
</tr>
<tr>
<td>Postoperative bradycardia</td>
<td>354 vs 318</td>
<td>RR = 1.44 (0.31-6.71)</td>
<td>.64</td>
<td>65</td>
</tr>
<tr>
<td>Urine output</td>
<td>190 vs 164</td>
<td>SMD = 0.01 (−0.27 to 0.28)</td>
<td>.95</td>
<td>35</td>
</tr>
<tr>
<td>Time to extubation (h)</td>
<td>469 vs 429</td>
<td>MD = −0.26 (−0.87 to 0.34)</td>
<td>.40</td>
<td>39</td>
</tr>
<tr>
<td>ICU stay (h)</td>
<td>498 vs 462</td>
<td>MD = −2.29 (−5.56 to 0.97)</td>
<td>.17</td>
<td>68</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>256 vs 219</td>
<td>MD = −0.05 (−0.43 to 0.33)</td>
<td>.81</td>
<td>0</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>371 vs 366</td>
<td>RR = 0.34 (0.11-1.07)</td>
<td>.06</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; DEX, dexmedetomidine; ICU, intensive care unit; MD, mean difference; RR, risk ratio; SMD, standard mean difference. * Indicates a statistically significant value.
LOS, or in-hospital mortality. The GRADE level of evidence was high for most of the outcomes.

Recently, 1 meta-analysis that included 10 studies showed that perioperative use of DEX may reduce the incidence of CS-AKI in adult patients. Although that work highlights potential benefits of DEX on CS-AKI, there are some concerns in the analysis approach and the eligibility of the included studies. First, the study of Balkanay in 2015 was split into 2 studies in analysis. Unfortunately, 28 patients in the control group were counted twice as 2 control arms in the pooled results, which created a unit-of-analysis error. Next, 3 studies did not report a specific outcome on AKI, but rather the events of renal failure in 2 studies and dialysis in the other. There may be some discrepancy among the incidence of renal failure, dialysis, and AKI. As a result, these 3 studies were excluded from this meta-analysis.

Clinical and animal studies have shown the protective effects of DEX against CS-AKI. Compared with saline, DEX reduced the level of plasma pro-inflammatory cytokines including tumor necrosis factor-α and interleukin-1β and reduced plasma norepinephrine and cortisol levels after cardiac surgery with CPB. In another study, DEX reduced the levels of serum urea nitrogen, creatinine, and neutrophil gelatinase-associated lipocalin but increased superoxide dismutase and intraoperative urine output. In the mice ischemia/reperfusion kidney injury model, pre- or post-treatment with DEX provided renoprotection by activating cell survival signaling phosphatidylinositol 3-kinase and inhibiting toll-like receptor 4 signaling. Another recent study showed that DEX protected against AKI in rats through the inhibition of apoptosis and inflammation.
In this study, DEX was found to be associated with reduced risks of AKI, prolonged ventilation, pulmonary complications, and delirium; however, these benefits did not translate into a reduced length of stay in either the ICU or the hospital. A possible explanation is that 9 RCTs with a relatively limited number of patients may not be enough to detect such differences. Heterogeneity among the studies may be another contributing factor. In fact, there were trends toward shorter length of ICU stay (mean difference = −2.29 hours) and lower mortality rate (RR = 0.34) associated with DEX in the results. The incidence of postoperative hypotension and bradycardia are similar between the DEX and control groups. All patients included in this meta-analysis received a continuous infusion with a relatively lower dose of DEX (0.1-0.8 μg/kg/h). At this infusion rate, DEX does not induce bradycardia and hypotension, and most patients did not receive a bolus dose.

This meta-analysis has several strengths. First, the current literature was reviewed comprehensively and the most recent and well-designed RCTs were included. Second, there was low heterogeneity (I² = 30%) among studies for the primary outcome, which contributes to the reliability for interpreting the current findings. Third, TSA was applied further to evaluate the impact

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**Fig 4.** Sensitivity analysis of primary outcome and publication bias assessment. (A) Sensitivity analysis showing relative risk of remaining studies when the named study is omitted from meta-analysis; (B) Begg’s funnel plot. RR, risk ratio; s.e., standard error.
of repetitive testing and random errors, which helps to provide a more conservative estimate. The TSA result suggest that enough evidence was reached and no further studies would be needed.

Fourth, the level of evidence was high for most of the outcomes including CS-AKI based on the GRADE profile.

Several limitations also exist. First, although pooling data of relevant studies by using a meta-analysis reduces the risk of type II error (a false negative finding), some inherent limitations for a meta-analysis includes heterogeneity among studies and publication bias. Some studies showed consistency in significant findings between meta-analyses and subsequent large RCTs, while other studies found a poor agreement. The TSA and GRADE methodology are useful to assess the robustness of the conclusion and determine the level of evidence. Second, the definition of AKI was not uniform across studies, which may have introduced bias. Third, with the primary outcome of CS-AKI, this meta-analysis may be underpowered to detect the difference in other outcomes, including postoperative complications, urine output, length of ICU stay, LOS, or in-hospital mortality. Fourth, the raw data were not available for the included trials, which precluded evaluating the effects of DEX use on CS-AKI at an individual patient level. Fifth, the lack of intention-to-treat analysis in the included studies makes it difficult to assess the overall effect of DEX treatment. Last, the overall number of patients included in this meta-analysis remains small, especially for more important and patient-centered outcomes. Therefore, based on the current results, the authors call for multicenter studies with larger sample sizes to confirm the effect of DEX on CS-AKI as well as to investigate whether any short-term effect on AKI could translate into a meaningful longer-term benefit.

**Conclusion**

This meta-analysis reveals evidence that perioperative administration of DEX reduces the incidence of CS-AKI in
### Table 3
GRADE Evidence Profile

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative AKI</td>
<td>9</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁⨁⨁⨁  High</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absolute (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.60 (0.41-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73 fewer per 1,000 (from 108 fewer to 24 fewer)</td>
<td>⨁⨁⨁      Moderate</td>
<td>Important</td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>3</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁⨁⨁      Moderate</td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.36 (0.20-0.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>91 fewer per 1,000 (from 114 fewer to 50 fewer)</td>
<td>⨁⨁⨁      High</td>
<td>Critical</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>3</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁⨁⨁      Moderate</td>
<td>Important</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.55 (0.31-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42 fewer per 1,000 (from 65 fewer to 4 fewer)</td>
<td>⨁⨁⨁      High</td>
<td>Critical</td>
</tr>
<tr>
<td>Delirium</td>
<td>4</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁⨁⨁      High</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.54 (0.32-0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay (h)</td>
<td>5</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁⨁◯◯  Important</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR - (0.00-0.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>3</td>
<td>Randomized</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁◯◯◯  Important</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td>* I</td>
<td></td>
<td></td>
<td></td>
<td>RR - (0.43-0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>4</td>
<td>Randomized</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>Relative (95% CI)</td>
<td>⨁◯◯◯  Important</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.34 (0.11-1.07)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; DEX, dexmedetomidine; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; MD, mean difference; RR, risk ratio.

* Heterogeneity ($I^2 = 68$) was found.

| Two trials were judged to be at unclear risk of bias.
adult patients. In addition, DEX use may be associated with reduced pulmonary complications and delirium without significant adverse effects. Further trials with large sample sizes and the use of intention-to-treat analysis are encouraged to verify the current findings.

Conflicts of Interest

All authors have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2019.09.011.

References