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Original Article

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 ≥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.

Key Words: dexmedetomidine; cardiac surgery; acute kidney injury; meta-analysis; trial sequential analysis

ACUTE KIDNEY injury (AKI) is common, affecting 5% to 7% of all hospitalizations and causing $10 billion of additional healthcare-related expenditures per year through per-hospitalization excess costs of $7,933.[1] Acute kidney injury occurs in 20% to 70% of patients who undergo cardiac surgery and is associated with up to a 60% mortality rate.[2,3] The potential etiologies for cardiac surgery-associated acute kidney injury (CS-AKI) include ischemia/reperfusion injury to the kidney,

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hemodynamic disturbance, inflammation, and especially exposure of blood to the cardiopulmonary bypass (CPB) circuit.[3,4] 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.[5] Studies suggest that DEX may provide renal protection for patients undergoing cardiac surgery.[6-9] 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.[10] To date, there are 2 meta-analyses that evaluated the effects of DEX on CS-AKI.[11,12] However, 1 meta-analysis included only 3 randomized controlled trials (RCTs) as well as 4 cohort studies, leading to a low level of evidence for the outcomes.[11] The other meta-analysis failed to include the most recent RCT,[8] 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.[13,14] 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.[15,16] 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 RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, 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 I^2 statistic, and $I^2 > 50\%$ 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 statistical 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-positive 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 diagram, a cumulative Z curve that crosses the trial sequential monitoring boundary or the futility boundary indicates a sufficient 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 versus 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 analyses, the primary outcome was stratified by time of intervention (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 procedures 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 criteria, 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.[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 compared to the control group (10.9% *v* 18.3%; RR = 0.60, 95% CI = 0.41-0.87, p = 0.008, $I^2 = 30\%$; 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 incidence ranged from RR = 0.48 (95% CI = 0.33-0.71) by omitting Li (2017) to RR = 0.67 (95% CI = 0.45-1.00) by omitting Cho (2016), indicating that no single study significantly

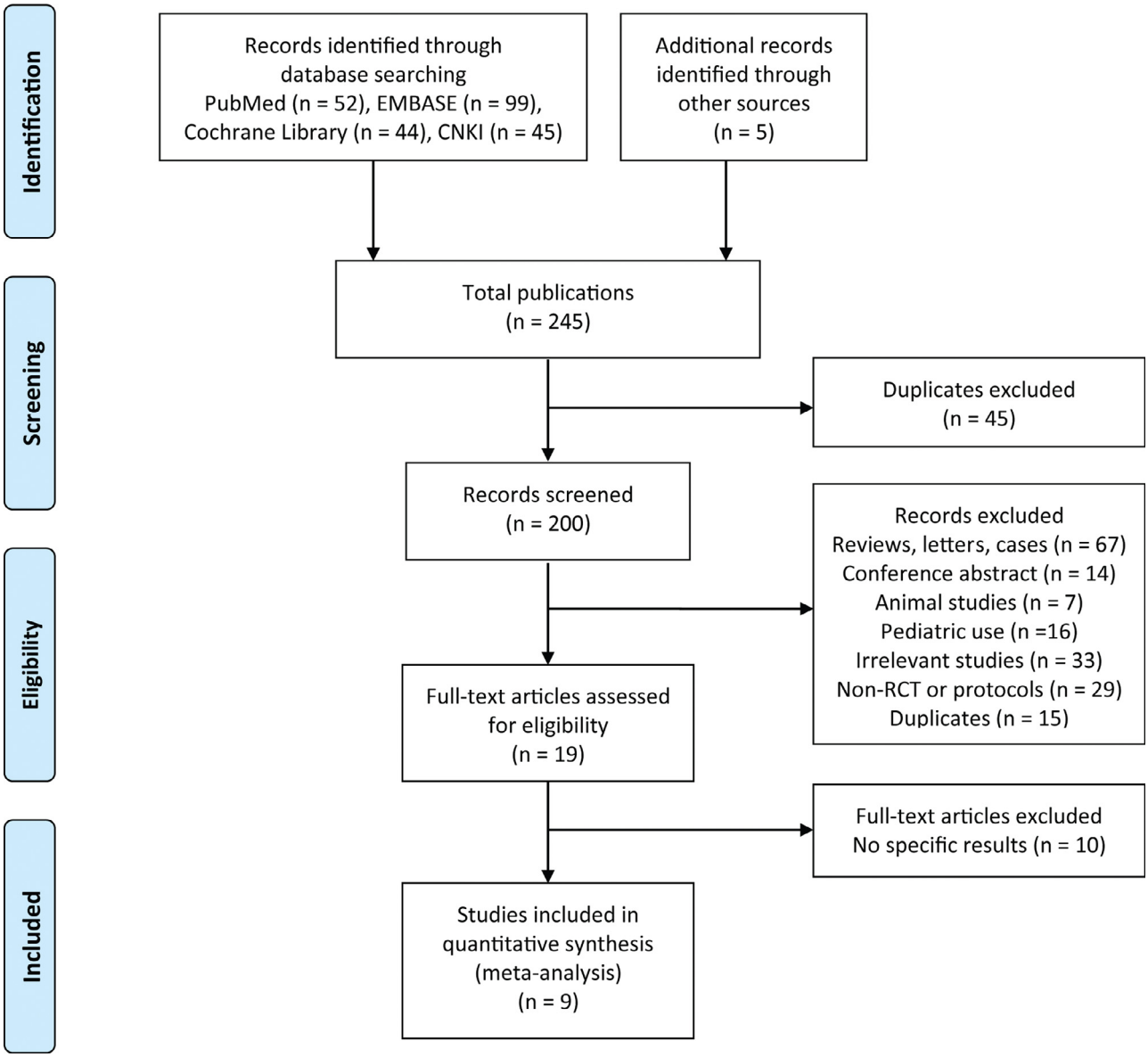

Fig 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial.

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

Table 1
Study Characteristics

Studies	Country	Group (Number of Patients)	Age (y)	Surgery	Time of Intervention	AKI Definition	Main Outcomes
Balkanay et al.,[8] 2015	Turkey	1. DEX <8 μg/kg (31) 2. DEX ≥8 μg/kg (29) 3. Saline (28)	60	On-pump CABG	Postoperative sedation for 24 h	RIFLE	AKI, urine output, time to extubation, delirium, atrial fibrillation, reoperation, hypotension, bradycardia, hospital and ICU stay
Cho et al.,[5] 2016	Korea	1. DEX 0.4 μg/kg/h (100) 2. Saline (100)	64 62	Cardiac surgery with CPB	After induction, until postoperative 24 h	AKIN	AKI, urine output, prolonged ventilation, pulmonary complication, infection, reoperation, ICU stay, mortality
Leino et al.,[6] 2011	Finland	1. DEX 0.6 ng/mL (35) 2. Saline (31)	59 62	On-pump CABG	After induction, until postoperative 4 h	RIFLE	AKI, time to extubation
Li et al.,[22] 2017	China	1. DEX 0.1-0.6 μg/kg/h (143) 2. Saline (142)	66 67	CABG and/or valve replacement	Before induction, until the end of ventilation	KDIGO	AKI, prolonged ventilation, infection, delirium, time to extubation, pulmonary complication, hypotension, bradycardia, ICU stay, mortality
Liu et al.,[23] 2016	China	1. DEX 0.2-1.5 μg/kg/h (44) 2. Propofol 0.3-3 mg/kg/h (44)	53 56	Cardiac surgery with CPB	Postoperative sedation until extubation	AKIN	AKI, prolonged ventilation, time to extubation, delirium, atrial fibrillation, hospital and ICU stay, mortality
Shehabi et al.,[24] 2009	Australia	1. DEX 0.1-0.7 μg/kg/h (152) 2. Morphine 10-70 μg/kg/h (147)	71 71	Cardiac surgery with CPB	Postoperative sedation until chest drain removal	sCr >2.0 times baseline	AKI, time to extubation, infection, delirium, atrial fibrillation, reoperation, hypotension, bradycardia, hospital and ICU stay, mortality
Soliman et al.,[25] 2016	Egypt	1. DEX 1 μg/kg + 0.3 μg/kg/h (75) 2. Saline (75)	58 57	Aortic vascular surgery	Before induction, until the end of surgery	sCr >115 μmol/L	AKI, pulmonary complication, hypotension, bradycardia, mortality
Wu et al.,[26] 2018	China	1. DEX 0.4-0.8 μg/kg/h (30) 2. Saline (30)	48 49	Valve replacement with CBP	Before induction, until the end of surgery	KDIGO	AKI
Zhai et al.,[7] 2017	China	1. DEX 0.6 μg/kg + 0.2 μg/kg/h (36) 2. Saline (36)	45 47	Valve replacement with CBP	Before induction, until the end of surgery	RIFLE	AKI, urine output, time to extubation

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.

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.

GRADE Evidence Profile

The GRADE evidence profile is outlined in Table 3. The level of evidence was high for most of the outcomes including postoperative CS-AKI, prolonged ventilation, pulmonary complications, delirium, and in-hospital mortality. For length of ICU stay and length of stay (LOS), the level of evidence was graded as moderate.

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,

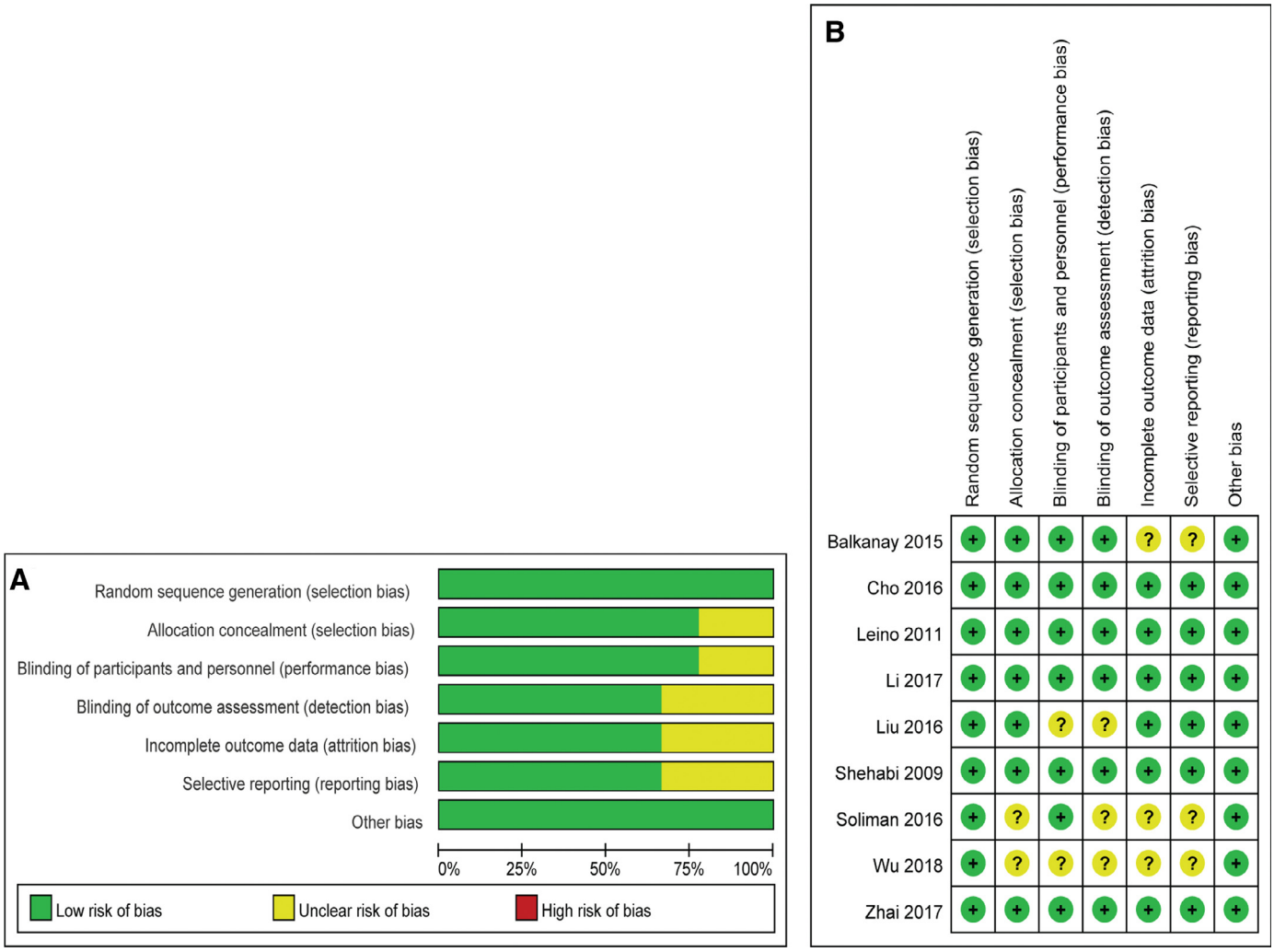

Fig 2. Risk of bias assessment. (A) Risk of bias graph; (B) risk of bias summary.

Table 2
Primary and Secondary Outcomes

Outcomes	DEX vs Control (n)	SMD, MD, or RR (95% CI)	p Value	I^2 (%)
Primary outcome				
Postoperative AKI	671 vs 633	RR = 0.60 (0.41-0.87)	.008*	30
Secondary outcomes				
Prolonged ventilation	286 vs 287	RR = 0.36 (0.20-0.65)	.0007*	0
Pulmonary complications	317 vs 318	RR = 0.55 (0.31-0.96)	.04*	0
Delirium	398 vs 362	RR = 0.54 (0.32-0.90)	.02*	0
Atrial fibrillation	256 vs 219	RR = 0.53 (0.26-1.09)	.08	58
Wound infection	394 vs 390	RR = 1.01 (0.36-2.80)	.99	46
Reoperation	312 vs 275	RR = 0.75 (0.34-1.62)	.46	0
Postoperative hypotension	354 vs 318	RR = 0.89 (0.36-2.19)	.79	84
Postoperative bradycardia	354 vs 318	RR = 1.44 (0.31-6.71)	.64	65
Urine output	196 vs 164	SMD = 0.01 (−0.27 to 0.28)	.95	35
Time to extubation (h)	469 vs 429	MD = −0.26 (−0.87 to 0.34)	.40	39
ICU stay (h)	498 vs 462	MD = −2.29 (−5.56 to 0.97)	.17	68
Hospital stay (d)	256 vs 219	MD = −0.05 (−0.43 to 0.33)	.81	0
In-hospital mortality	371 vs 366	RR = 0.34 (0.11-1.07)	.06	0

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.

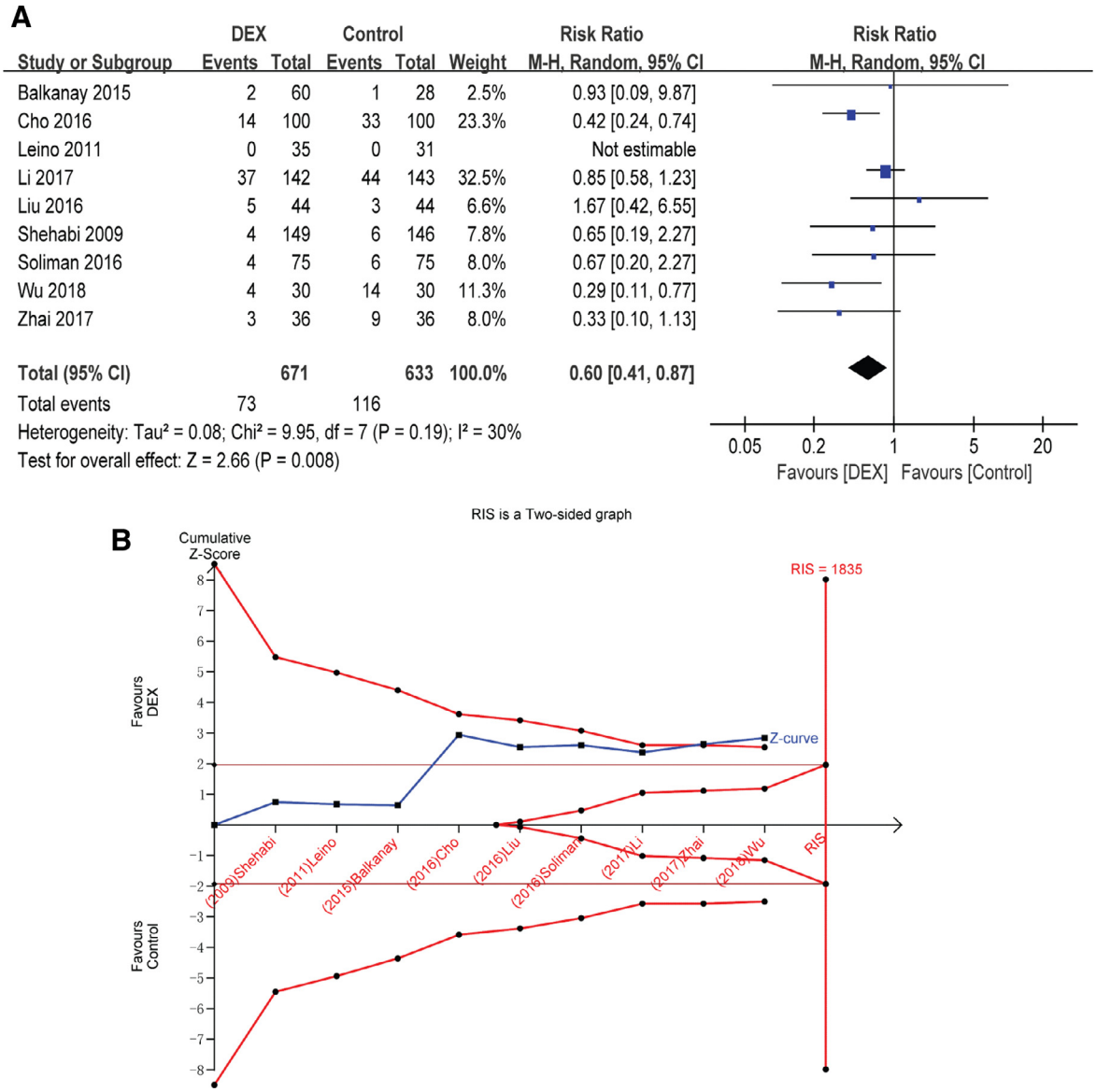

Fig 3. DEX versus control for acute kidney injury after cardiac surgery. (A) Incidence of postoperative acute kidney injury; (B) trial sequential analysis. DEX, dexmedetomidine; RIS, required information size.

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.[12] 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.[9] 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.[28-30] 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.[28] 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.[8] 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.[31] Another recent study showed that DEX protected against AKI in rats through the inhibition of apoptosis and inflammation.[32]

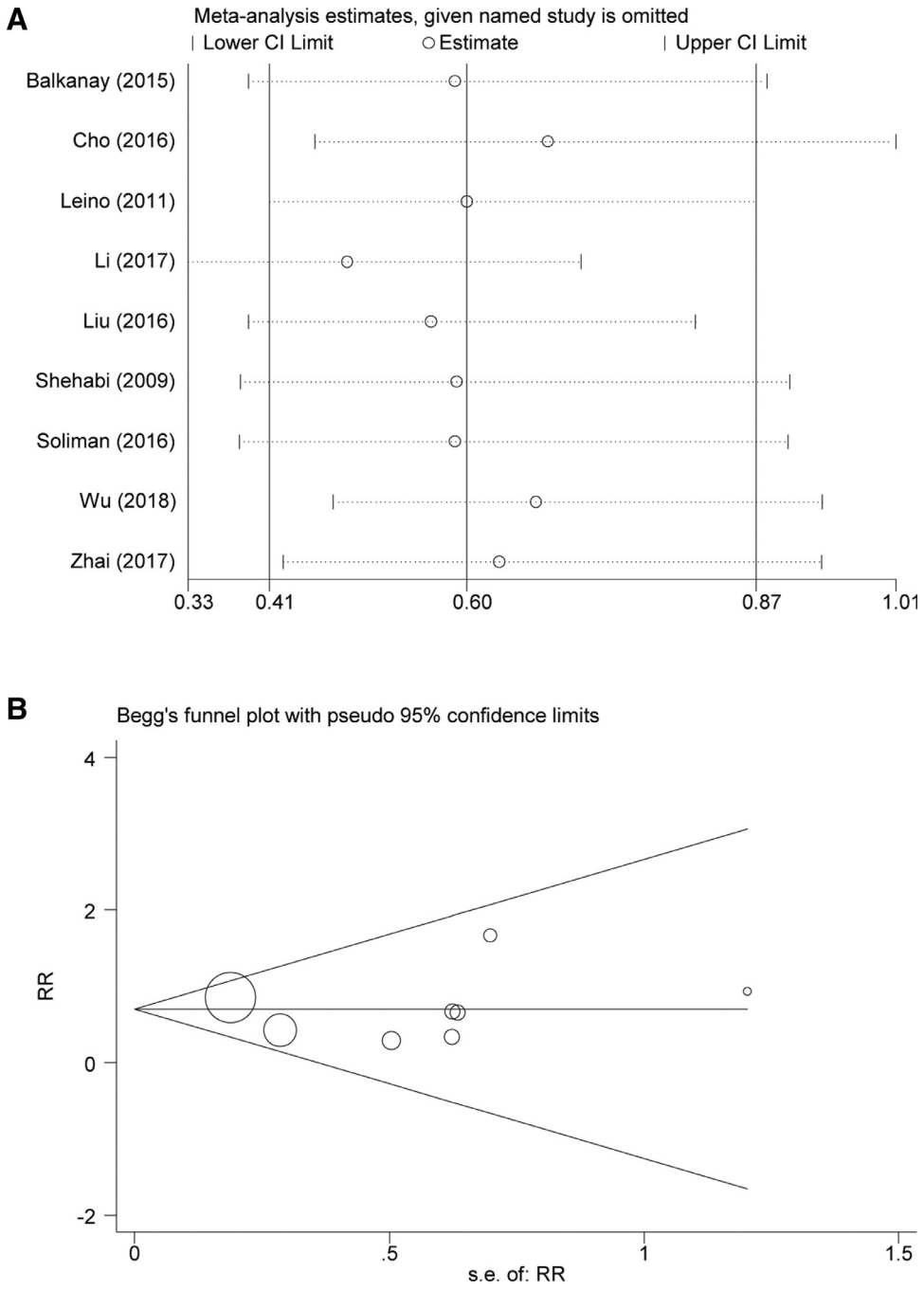

Fig 4. Sensitivity analysis of primary outcome and publication bias assessment. (A) Sensitivity analysis showing relative risk of remaining studies when the named study is omitted from meta-analysis; (B) Begg's funnel plot. RR, risk ratio; s.e., standard error.

In this study, DEX was found 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 ($I^2 = 30\%$) 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

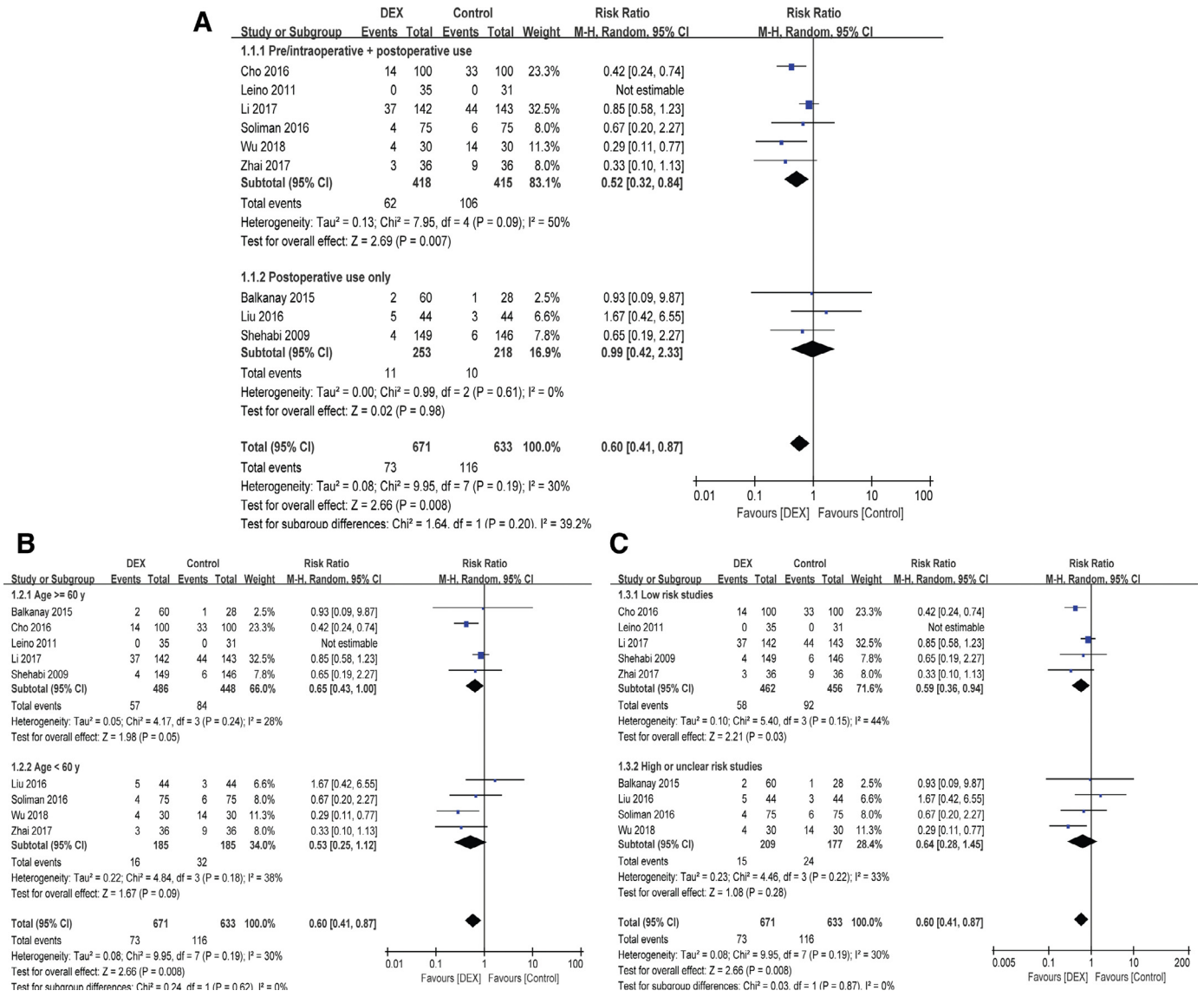

Fig 5. Subgroup analysis of primary outcome. (A) Preoperative and/or intraoperative initiation with or without postoperative continuation of DEX versus postoperative use only; (B) age ≥60 years versus age <60 years; (C) low risk of bias studies versus high or unclear risk of bias studies. DEX, dexmedetomidine.

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,[33,34] while other studies found a poor agreement.[35,36] 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

Certainty Assessment							Number of Patients		Effect		Certainty	Importance
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	DEX	Control	Relative (95% CI)	Absolute (95% CI)		
Postoperative AKI												
9	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	73/671 (10.9%)	116/633 (18.3%)	RR 0.60 (0.41-0.87)	73 fewer per 1,000 (from 108 fewer to 24 fewer)	⊕⊕⊕⊕ High	Critical
Prolonged ventilation												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	14/286 (4.9%)	41/287 (14.3%)	RR 0.36 (0.20-0.65)	91 fewer per 1,000 (from 114 fewer to 50 fewer)	⊕⊕⊕⊕ High	Critical
Pulmonary complications												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	16/317 (5.0%)	30/318 (9.4%)	RR 0.55 (0.31-0.96)	42 fewer per 1,000 (from 65 fewer to 4 fewer)	⊕⊕⊕⊕ High	Critical
Delirium												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	20/398 (5.0%)	39/362 (10.8%)	RR 0.54 (0.32-0.90)	50 fewer per 1,000 (from 73 fewer to 11 fewer)	⊕⊕⊕⊕ High	Critical
ICU stay (h)												
5	Randomized trials	Not serious	serious [a]	Not serious	Not serious	None	498	462	-	MD 2.29 lower (5.56 lower to 0.97 higher)	⊕⊕⊕ Moderate	Important
Hospital stay (d)												
3	Randomized trials	Serious [*,†]	Not serious	Not serious	Not serious	None	256	219	-	MD 0.05 lower (0.43 lower to 0.33 higher)	⊕⊕⊕ Moderate	Important
In-hospital mortality												
4	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	3/371 (0.8%)	11/366 (3.0%)	RR 0.34 (0.11-1.07)	20 fewer per 1,000 (from 27 fewer to 2 more)	⊕⊕⊕⊕ High	Critical

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.

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