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Perioperative dexmedetomidine administration does not reduce the risk of acute kidney injury after non-cardiac surgery: a meta-analysis

Bin Hu, Tian Tian, Xintao Li, Weichao Liu, Yinggui Chen, Tianyu Jiang, Peishan Chen, Fushan Xue

Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China.

Abstract

Background: Post-operative acute kidney injury (AKI) is one of the most common and serious complications after major surgery and is significantly associated with increased risks of morbidity and mortality. This meta-analysis was conducted to evaluate the effects of perioperative dexmedetomidine (Dex) administration on the occurrence of AKI and the outcomes of recovery after non-cardiac surgery.

Methods: The PubMed, Embase, Web of Science, and Cochrane Library databases were systematically searched for studies comparing the effects of Dex *vs.* placebo on kidney function after non-cardiac surgery, and a pooled fixed-effect meta-analysis of the included studies was performed. The primary outcome was the occurence of post-operative AKI. The secondary outcomes included the occurence of intra-operative hypotension and bradycardia, intensive care unit (ICU) admission, duration of ICU stay, and hospital length of stay (LOS).

Results: Six studies, including four randomized controlled trials (RCTs) and two observational studies, with a total of 2586 patients were selected. Compared with placebo, Dex administration could not reduce the odds of post-operative AKI (odds ratio [OR], 0.44; 95% confidence interval (CI), 0.18–1.06; $P = 0.07$; $I^2 = 0.00\%$, $P = 0.72$) in RCTs, but it showed a significant renoprotective effect (OR, 0.67; 95% CI, 0.48–0.95; $P = 0.02$; $I^2 = 0.00\%$, $P = 0.36$) in observational studies. Besides, Dex administration significantly increased the odds of intra-operative bradycardia and shortened the duration of ICU stay. However, there was no significant difference in the odds of intra-operative hypotension, ICU admission, and hospital LOS.

Conclusions: This meta-analysis suggests that perioperative Dex administration does not reduce the risk of AKI after non-cardiac surgery. However, the quality of evidence for this result is low due to imprecision and inconsistent types of non-cardiac operations. Thus, large and high-quality RCTs are needed to verify the real effects of perioperative Dex administration on the occurrence of AKI and the outcomes of recovery after non-cardiac surgery.

Keywords: Dexmedetomidine; Non-cardiac surgery; Acute kidney injury; Meta-analysis

Introduction

Acute kidney injury (AKI) is a common and serious complication after major non-cardiac surgery, which is associated with increased renal replacement therapy (RRT) requirements, extended hospital length of stay (LOS), increased medical expenses, and raised in-hospital morbidity and mortality.[1,2] It has been reported that AKI occurs in 20% to 70% of patients receiving cardiac surgery[3,4] and 6.1% to 22.4% of patients receiving major non-cardiac surgery.[5] Furthermore, age, comorbidities, pre-existing renal dysfunction, and types of surgery are known important risk factors for the occurrence of post-operative AKI.[6] It is generally believed that underlying mechanisms of post-operative AKI are multifactorial and are possibly related to sympathetic nervous system activation, oxidative stress, inflammatory responses, and the occurrence of ischemia/reperfusion injury (IRI).[7] Numerous perioperative interventions, such as remote ischemic preconditioning,[8,9] pharmacological treatments,[10] optimized fluid therapy, and renal perfusion,[11] have been attempted to prevent or decrease the occurrence of post-operative AKI, but their clinical effects remain controversial. Along with the increasing high risk of the surgical population, such as advanced age, diabetes mellitus (DM), and pre-existing renal damage, post-operative AKI has become one of the main problems endangering perioperative safety of surgical patients. Thus, in 2019, a joint meeting of the Acute Disease Quality Initiative (ADQI-24) and the PeriOperative Quality Initiative (POQI-7) was convened to address AKI after major non-cardiac surgery. In 2021, the Expert Committee published a consensus that was achieved in this meeting, that is, the joint consensus report of post-operative AKI in

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Correspondence to: Prof. Fushan Xue, Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China
E-Mail: xuefushan@aliyun.com; fushanxue@outlook.com

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adult non-cardiac surgery. In this consensus report, the graded recommendations for AKI after non-cardiac surgery are provided and the priorities for future research are highlighted.[12]

Dexmedetomidine (Dex), a highly selective α2-adrenergic agonist with sedation, analgesia, and anti-inflammation effects, has been widely used for surgical and intensive care unit (ICU) patients.[13] A number of basic studies have indicated the advantage of Dex in alleviating renal damage by inhibiting apoptosis and inflammation,[14] activating cell survival signaling phosphatidylinositol 3-kinase, and inhibiting the toll-like receptor 4 signaling pathway.[15] Furthermore, many studies have shown the potential benefits of Dex for cardiac surgery-associated AKI. In a recent meta-analysis including ten randomized controlled trials (RCTs) with 1575 patients, perioperative Dex administration significantly reduced the incidence of post-operative AKI in adult patients undergoing cardiac surgery.[16] However, a few studies have assessed the effects of perioperative Dex administration on the occurrence of AKI after non-cardiac surgery and inconsistent results have been achieved.[17-19] Thus, it remains unclear whether perioperative Dex administration can reduce the risk of post-operative AKI in patients undergoing non-cardiac surgery. To resolve this issue, this meta-analysis was designed to systematically evaluate the effects of perioperative Dex administration on the occurrence of AKI and the outcomes of recovery after non-cardiac surgery.

Methods

Data source and search strategy

There was no registered protocol for this meta-analysis. A comprehensive review of the published literature was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[20] We performed a systematic search in the PubMed, Embase, Web of Science, and Cochrane library databases for the evidence of perioperative Dex administration to reduce the risk of AKI after non-cardiac surgery using the MeSH terms "dexmedetomidine," "acute kidney injury", and corresponding entry terms published from the inception to May 2022 [Supplementary material 1, http://links.lww.com/CM9/B236]. The language of articles was restricted to English.

Literature review and inclusion criteria

Two independent investigators (Bin Hu and Tian Tian) screened the results of literature search to identify and determine the relevant studies. The eligibility criteria were as follows: (1) the study design was either RCTs or observational studies; (2) the patients underwent non-cardiac surgery; (3) the perioperative interventions consisted of Dex and were compared with placebo; (4) the outcome included the incidence of post-operative AKI, which was defined by Kidney Disease: Improving Global Outcome (KDIGO), Acute Kidney Injury Network (AKIN), or other internationally recognized criteria. The exclusion criteria were as follows: (1) the incidence of AKI in the control group was not reported; (2) basic experimental study; (3) non-English report.

Data extraction

For studies that met the selection criteria, two review authors (Bin Hu and Tian Tian) independently extracted the following data: first author, publication year, country, age, gender composition, study design, incidence of AKI, Dex dose and usage, clinical endpoints, and AKI definition. Any discrepancy at this step was resolved by re-examination of the data and a consensus with the other review authors.

Post-operative outcomes

The primary outcome was the occurence of post-operative AKI, defined by the KDIGO, AKIN, or other internationally recognized criteria. Secondary outcomes included the occurence of intra-operative hypotension and bradycardia, ICU admission, duration of ICU stay, and hospital LOS.

Quality assessment

Using the Cochrane risk of bias tool,[21] 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 any other bias. The quality of observational study was assessed using the Risk Of Bias In Non-randomized Studies (ROBINS-I) tool,[22] which evaluated the possibility of bias due to confounding, selection, classification, deviation from intended intervention, missing data, measurement, and reporting of the outcomes. Any potential disagreement was resolved through consensus of all authors.

Subgroup analysis

One review author further evaluated the potential sources of heterogeneity of the primary outcome for RCTs using subgroup analysis. The results were checked by other two authors. In the subgroup analysis, the primary outcome was stratified by country (China *vs.* Korea), AKI definitions (KDIGO *vs.* other), proportion of males (≥ 50% *vs.*<50%), proportion of patients with DM (≥ 10% *vs.*<10%), and endoscopy surgery (Yes *vs.* No).

Statistical analysis

For dichotomous outcomes, the odds ratio (OR) with 95% confidence interval (CI) was calculated. For continuous outcomes reported as mean ± standard deviation, median and interquartile range (IQR), or median and range, mean differences for each study were calculated according to the statistical method proposed by Wan *et al*[23] and the weight (the inverse variance of the estimate) was used to pool the estimate (weighted mean difference, WMD) with 95% CI. A fixed-effect model was used to pool all the data. Heterogeneity was evaluated using the I^2 statistic, and the percentage of I^2 indicated the degree of heterogeneity. I^2 percentages of 25%, 50%, and

75% indicated low, medium, and high heterogeneity,[24] respectively, and $P < 0.1$ indicated significant heterogeneity. Publication bias was assessed by the Begg's test and Egger's test. Statistical analyses were performed with the Review Manager software version 5.3 (Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen, Denmark) and STATA version 17.0 (STATA Corporation, College Station, TX, USA). GraphPad Prism for Windows (Version 9, GraphPad Software Inc., San Diego, CA, USA) was used for production of figures. A P value less than 0.05 was considered statistically significant.

Results

Study selection

Our initial search identified 562 records. After 177 duplicate reports were excluded, a total of 385 reports underwent title and abstract screening. This resulted in further exclusion of 376 reports, including 175 irrelevant studies; 80 pre-clinical studies; 68 reviews, meta-analysis, and letters; 42 cardiac surgeries; 1 protocol and 1 conference abstract; and 9 register records without published results. The remaining 9 reports were retrieved for evaluation of detailed full text. As a result, three articles were further excluded because two articles did not report AKI and one article did not include placebo. Eventually, six literatures containing four RCTs and two retrospective cohort studies met our selection criteria and were included in the quantitative synthesis. Of the six included studies, four RCTs were carried out in patients undergoing the percutaneous nephrolithotomy lithotripsy,[17] cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy,[25] laparoscopic radical prostatectomy,[26] and laparoscopic colorectal cancer,[18] respectively. One retrospective cohort study was performed in patients who underwent lung cancer surgery[27] and the other study was performed in patients who underwent major joint replacement.[19] A flow diagram of the included and excluded studies for the meta-analysis is presented in Figure 1. For the Dex intervention regimen, all four RCTs included a loading dose and a subsequent continuous infusion dose, that is, 1.0 μg/kg of Dex was intravenously administered before or after anesthesia induction and was followed by continuous infusion at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ during the operation. In the two retrospective cohort studies, Dex was continuously infused at a rate of 0.2 to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in one study[27] and was intravenously administered with a loading dose of 0.5 to 1.0 μg/kg within 10 to 15 min or intra-operative continuous infusion was performed at a rate of 0.2 to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in another study.[18] The main characteristics and demographics of the subjects of the included studies are presented in Table 1.

Meta-analysis of outcomes

Six included studies comprised 2586 participants for comparisons. The meta-analysis showed that peri-operative Dex administration could not reduce the odds of AKI (8/186 *vs.* 17/187; OR, 0.44; 95%CI, 0.18–1.06; $P = 0.07$; $I^2 = 0.00\%$, $P = 0.72$) in RCTs [Supplementary Figure 1, http://links.lww.com/CM9/B233], but it was

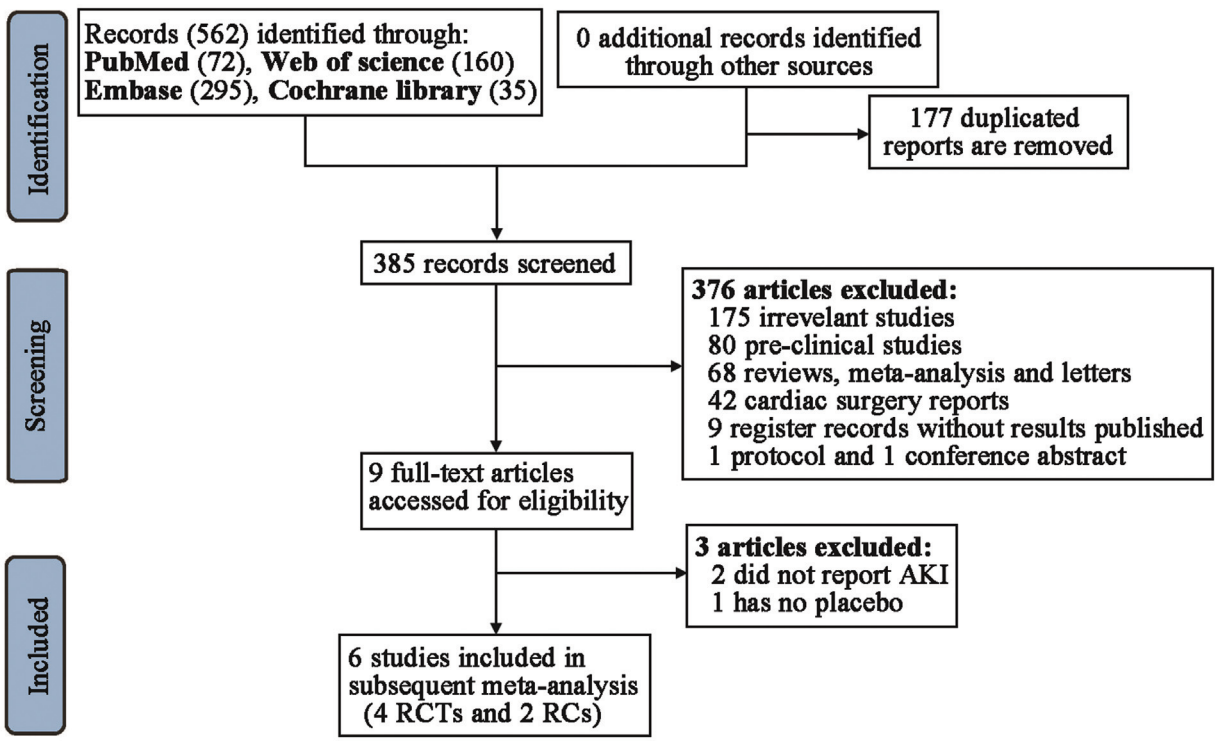

Figure 1: A flow chart of the included and excluded studies for the meta-analysis. AKI: Acute kidney injury; RCTs: Randomized controlled trails; RC: Retrospective cohort.

Table 1: The characteristics of studies included in the meta-analysis.

Study	Country	Surgery	Age (years)	Gender (male/total)	Incidence of AKI		Dexmedetomidine dose	Clinical endpoints	AKI definitions
					Control	Dexmedetomidine			
Randomized Controlled Trial									
Deng 2018	China	Percutaneous nephrolithotomy lithotripsy	≥20 and ≤75	85/190	3/95	3/95	Loading: 1 μg/kg Maintenance: 0.5 μg·kg^{-1}·h^{-1}	AKI, Hospital LOS Hypotension, Bradycardia	NA
Song 2019	Korea	CRS and HIPEC	≥20	21/38	5/19	2/19	Loading: 1 μg/kg Maintenance: 0.5 μg·kg^{-1}·h^{-1}	AKI, ICU stay, Hospital LOS	KDIGO
Wu 2019	China	Laparoscopic radical prostatectomy	≥60 and ≤79	89/89	6/45	2/44	Loading: 1 μg/kg Maintenance: 0.5 μg·kg^{-1}·h^{-1}	AKI, Hospital LOS, Bradycardia	KDIGO
Sun 2021	China	Laparoscopic surgery for colorectal cancer	≥18 and ≤65	36/56	3/28	1/28	Loading: 1 μg/kg Maintenance: 0.5 μg·kg^{-1}·h^{-1}	AKI, Hospital LOS	KDIGO
Observational Study									
Moon 2016	America	Lung cancer surgery	≥18	629/1207	80/949	18/258	Maintenance: 0.2 –0.7 μg·kg^{-1}·h^{-1}	AKI	AKIN
Zhu 2020	China	Major joint replacement	≥65	406/1006	58/503	36/503	Loading: 0.5–1.0 μg/kg or Maintenance: 0.2–0.7 μg·kg^{-1}·h^{-1}	AKI, ICU admission, Hospital LOS, Hypotension, Bradycardia	KDIGO

The study ID is represented by last name of first author and year of publication. AKI: Acute kidney injury; AKIN: Acute Kidney Injury Network; CRS and HIPEC: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; ICU: Intensive care unit; KDIGO: Kidney Disease: Improving Global Outcome; LOS: Length of stay.

associated with decreased odds of AKI [54/761 *vs.* 138/1452; OR, 0.67; 95%CI, 0.48–0.95; $P = 0.02$; $I^2 = 0.00\%$, $P = 0.36$] in observational studies [Supplementary Figure 2, http://links.lww.com/CM9/B234]. Furthermore, there was no evidence of significant publication bias in RCTs (Begg's test, $P = 1.00$; Egger's test, $P = 0.56$).

Subgroup analysis of RCTs for the potential sources of heterogeneity are listed in Supplementary Table 1, http://links.lww.com/CM9/B237. The study participants were divided into five groups according to different characteristics, such as country (China *vs.* Korea), AKI definitions (KDIGO *vs.* other), proportion of males (≥50% *vs.* < 50%), proportion of patients with DM (≥10% *vs.* <10%), and endoscopy surgery (Yes *vs.* No). Overall, there were no significant between-group differences in the odds of AKI [Supplementary Table 1, http://links.lww.com/CM9/B237].

For secondary outcomes reported in several studies, the results of RCTs and observational studies were separated to present. Perioperative Dex administration significantly increased the odds of intra-operative bradycardia in both RCTs (OR, 2.82; 95%CI, 1.66 to 4.77, $P<0.01$) and observational studies (OR, 1.41; 95%CI, 1.02 to 1.96, $P = 0.04$) [Table 2]. However, there was no significant difference in the odds of intra-operative hypotension between RCTs (OR, 1.47; 95%CI, 0.73 to 2.96, $P = 0.29$) and observational studies (OR, 1.14; 95%CI, 0.83 to 1.57, $P = 0.42$) [Table 2].

For secondary outcomes only reported in one study, OR or WMD was calculated to compare the difference between the two groups in this study. Perioperative Dex administration significantly shortened the duration of ICU stay (WMD, −1.00; 95%CI, −1.51 to −0.49, $P < 0.01$). Furthermore, there was a trend towards reduction of ICU admission with perioperative Dex use (OR, 0.86; 95% CI, 0.58–1.29; $P = 0.47$), although no statistically significant difference was achieved [Table 2].

Five studies (four RCTs and one retrospective cohort study, including five comparisons) reported hospital LOS, but the raw data of two studies (Wu *et al*[26] and Sun *et al*[18]) could not be obtained or calculated because only medians and IQR of hospital LOS were provided.[23] Thus, only three studies (two RCTs and one retrospective cohort study, including three comparisons) with 1234 participants were included in the analysis of hospital LOS. In the observational study, perioperative Dex administration was associated with a significant reduction in hospital LOS (WMD, −0.40; 95%CI, −0.64 to −0.16, $P = 0.001$). However, there was no significant difference in the hospital LOS in RCTs (WMD, −0.31; 95%CI, −1.28 to 0.66, $P = 0.53$; $I^2 = 52.1\%$, $P = 0.15$) [Table 2].

Risk of bias assessment

Two investigators (Bin Hu and Tian Tian) agreed on every item of the Cochrane risk of bias tool and the ROBINS-I tool. RCTs were evaluated with the Cochrane risk of bias tool [Supplementary Figure 3, http://links.lww.com/CM9/B235], and the observational studies were evaluated with

Table 2: Secondary outcomes of studies included in the meta-analysis.

Secondary outcome	Study design	Study	OR or WMD	95% CI	*P* value	I^2	*P* value
Hypotension	RCT	Deng 2018	1.47*	0.73, 2.96	0.29	NA	NA
	RC	Zhu 2020	1.14*	0.83, 1.57	0.42	NA	NA
Bradycardia	RCT	Deng 2018, Wu 2019	2.82*	1.66, 4.77	<0.01	0.0%	0.53
	RC	Zhu 2020	1.41*	1.02, 1.96	0.04	NA	NA
ICU admission	RC	Zhu 2020	0.86*	0.58, 1.29	0.47	NA	NA
ICU stay	RCT	Song 2019	–1.00†	–1.51, –0.49	<0.01	NA	NA
Hospital LOS	RCT	Deng 2018, Song 2019	–0.31†	–1.28, 0.66	0.53	52.1%	0.15
	RC	Zhu 2020	–0.40†	–0.64, –0.16	0.001	NA	NA

* OR. † WMD. CI: Confidence interval; ICU: Intensive care unit; LOS: Length of stay; NA: Not available; OR: Odds ratio; RC: Retrospective cohort; RCT: Randomized controlled trial; WMD: Weighted mean difference.

the ROBINS-I tool [Supplementary Table 2, http://links.lww.com/CM9/B238].

Discussion

The major purpose of this meta-analysis, including four RCTs and two observational studies with 2586 patients, was to evaluate the effect of perioperative Dex administration on the risk of AKI after non-cardiac surgery. The main results of this analysis showed that observational studies implied a potential benefit of Dex intervention in decreasing the risk of post-operative AKI after non-cardiac surgery, but RCTs did not prove this benefit. Similarly, a shortened hospital LOS with perioperative Dex use was noted in observational studies, but this result was not found in RCTs. In addition, perioperative Dex use was significantly associated with the occurrence of intraoperative bradycardia in both RCTs and observational studies.

Post-operative AKI is a common complication, which accounts for 18% to 47% of all hospital-acquired AKI.[28,29] To date, a number of research studies have focused on cardiac surgery-associated AKI. It has been reported that 15% of patients undergoing cardiac surgery develop AKI, and 2% of patients require RRT.[30] However, the occurrence and related adverse effects of AKI after non-cardiac surgery may have been underestimated.[4,12] In a study of 75,952 patients with a normal renal function undergoing non-cardiac surgery, Kheterpal *et al*[30] demonstrated that the incidence of post-operative AKI, defined as an increase in serum creatinine of at least 2 mg/dL or need for RRT, was about 1%, and patients with post-operative AKI have an eight-fold increase in mortality, independent of the underlying comorbidities. In fact, the incidence of AKI after non-cardiac surgery is comparable to that of other severe post-operative complications, such as venous thromboembolism and major adverse cardiac events.[30] Due to this reason, preventing or reducing the occurrence of AKI after non-cardiac surgery has become an important element of the initiatives to improve perioperative safety of surgical patients.[12]

Dex is a α2-adrenoceptor agonist with sedation, analgesia, and sympathicolysis effects.[31] To date, many animal and clinical studies have shown the protective effects of Dex against renal damage. In a mouse model of renal IRI, Dex provides renoprotection by ameliorating the inflammatory response[15] and apoptosis.[32] Moreover, in patients undergoing cardiac surgery, perioperative Dex administration has been significantly associated with a reduced incidence of post-operative AKI.[33,34] A retrospective study including 1133 patients undergoing cardiac surgery has also shown that Dex significantly reduces the overall incidence of post-operative AKI from 33.8% to 26.1% (OR 0.70; 95%CI 0.54–0.92).[35] However, it remains unclear whether perioperative Dex administration can reduce the risk of AKI after non-cardiac surgery.

Most of the studies included in this meta-analysis showed that perioperative Dex administration resulted in a trend towards decreasing the risk of AKI after non-cardiac surgery, but a statistically significant difference was not achieved.[18,25-27] In fact, of the six included studies, only one retrospective cohort study showed a significant renoprotective effect of perioperative Dex administration.[19] However, in a RCT with 190 patients undergoing percutaneous nephrolithotomy lithotripsy who were randomly assigned to receive either Dex or saline, Deng *et al*[17] demonstrated that Dex could not reduce the incidence of post-operative AKI. Although the pooled meta-analysis result of two observational studies suggested that perioperative Dex intervention was associated with a significantly decreased risk of post-operative AKI, all four RCTs did not show this beneficial effect of Dex. This indicates that the significant renoprotective effect of perioperative Dex administration in this meta-analysis was mainly attributable to the results of the retrospective cohort study reported by Zhu *et al*[19]. Nevertheless, this was a single-center retrospective cohort study with many limitations; for example, some important confounders associated with the development of post-operative AKI, details of anesthesia management, and usage and dose of Dex were not provided. In fact, compared with the RCT, the observational studies were highly subject to unknown confounders, such as age, gender, comorbidities, and others. In such instances when the known or suspected confounders are ignored, the regression estimates of treatment effect would be biased, leading to an omitted variable or residual confounding bias.[36] It must be emphasized that observational studies can serve as supplementary evidence in addition to the RCTs. However, when the results of observational studies and RCTs are inconsistent, combined results from RCTs

should be addressed first and regarded as the primary findings. Thus, combined findings of this meta-analysis are inadequate to prove the beneficial effect of Dex in reducing the occurrence of AKI after non-cardiac surgery. As the gold standard tool to evaluate the safety and efficacy of an intervention, we believe that well-designed RCTs with large samples are required to determine the real effects of perioperative Dex administration on the occurrence of AKI after non-cardiac surgery. If further studies demonstrate a consistent beneficial effect of perioperative Dex administration on the occurrence of AKI after non-cardiac surgery, as indicated in observational studies, the clinical implications are immense.

Secondary outcomes of this meta-analysis included the occurence of intra-operative hypotension and bradycardia, ICU admission, duration of ICU stay, and hospital LOS. As already known, bradycardia is a common side effect of Dex. It was not surprising that Dex administration was found to significantly increase the odds of intra-operative bradycardia, either in randomized or observational studies.[17,19,26] Notably, although Dex was significantly associated with intra-operative bradycardia, the results showed that Dex did not increase the risk of intra-operative hypotension.[17,19] This suggests, to some extent, that the commonly used clinical dose of Dex does not cause hypotension leading to renal hypoperfusion and aggravating renal tissue damage. Besides, Yugeesh *et al*[37] demonstrated that Dex intervention could reduce norepinephrine requirements and preserve renal oxygenation and function in ovine septic AKI, and further offer renoprotection. In a retrospective cohort study with 1006 elderly patients undergoing major joint replacement, Zhu *et al*[19] found no significant between-group difference in ICU admission. However, in a RCT with 38 patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, Song *et al*[24] demonstrated that the duration of ICU stay was significantly shortened with perioperative Dex administration. In addition, similar to the finding of Dex in post-operative AKI, the results of Dex reducing hospital LOS were inconsistent between the RCTs and observational study;[17,19,25] i.e., the observational study confirmed that Dex could shorten the hospital LOS, but the RCTs showed a negative finding. Therefore, available evidence is inadequate to prove that perioperative Dex administration can shorten the hospital LOS after non-cardiac surgery. This result is similar to the findings of the meta-analysis by Liu *et al*,[16] in which perioperative Dex use could not shorten the duration of ICU stay and hospital LOS after adult cardiac surgery. Thus, the potential effects of perioperative Dex administration on these outcomes of recovery after non-cardiac surgery need future assessment by performing large RCTs.

Although the number of literature included in this meta-analysis is limited and four RCTs only included small simple sizes, our analysis has several strengths. First, it comprehensively reviewed the data of available literatures regarding the effect of perioperative Dex administration on the occurrence of AKI after non-cardiac surgery and showed no significance heterogeneity for the primary outcome among randomized studies ($I^2 = 0.00\%$, $P = 0.72$). Second, the results from the Cochrane risk of bias tool for RCTs and the ROBINS-I tool for observatiobal studies showed that the methodological quality of studies included in this meta-analysis had low bias. All of these factors contributed to reliable interpretation of our findings.

However, this meta-analysis has several limitations that deserve attention. First, a limited number of studies were included and the pooled raw data were only derived from four RCTs and two observational studies. These studies were performed in patients undergoing six types of different non-cardiac operations. It is generally believed that the type of operation is an important factor affecting the development of AKI after non-cardiac surgery.[12] Furthermore, all of the included RCTs were single-center studies, with relatively small sample sizes. These issues can undoubtedly decrease the level of evidence for the findings of this analysis. Third, two observational studies were included. The main limitation of an observational study is that many potential confounders may inevitably affect the results. Most importantly, an observational study cannot determine whether there is a causal relationship between the intervention and interested outcome because there are a variety of sources of bias, such as omitted variables, measurement error, sample selection bias, and various combinations of these problems. All of these factors can affect the causal inference of comparative treatment effects from non-randomized studies using secondary databases.[36] Fourth, other than the primary outcome, this meta-analysis was underpowered to detect the differences in other secondary outcomes, such as duration of ICU stay, ICU admission, and hospital LOS. Fifth, exclusion of studies published in non-English language may have resulted in the lack of inclusion of some important studies. Undoubtedly, all of the above factors can affect the strength of evidence for our results. Thus, large RCTs are needed to determine whether perioperative Dex administration can decrease the occurrence of AKI after non-cardiac surgery.

In summary, the available evidence is inadequate to prove that perioperative Dex administration can reduce the risk of AKI after non-cardiac surgery. However, the strength of evidence for our results might have been weakened by the limited number of included randomized studies, small simple size, and various study objectives. Thus, large and high-quality RCTs are needed to verify the benefit of perioperative Dex administration in decreasing the risk of AKI after non-cardiac surgery.

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Conflicts of interest

None.

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