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REVIEW ARTICLE

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# Efficacy of dexmedetomidine in prevention of junctional ectopic tachycardia and acute kidney injury after pediatric cardiac surgery: A meta-analysis

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## Abstract

**Objective**: We conducted a meta-analysis to evaluate the effects of prophylactic perioperative dexmedetomidine administration on postoperative junctional ectopic tachycardia (JET) and acute kidney injury (AKI) in pediatric patients having undergone cardiac surgery.

**Design**: This systematic review was registered with PROSPERO (CRD42017083880). Databases including PubMed, Cochrane Central Register of Controlled Trials, and Web of Science were searched for randomized controlled trials (RCTs) and observational cohort studies from its inception to March 2018. Two reviewers independently screened literature, extracted data, and assessed the quality of included studies using the Jadad scale and Newcastle-Ottawa score. Meta-analysis was then conducted by RevMan 5.3 and Stata 12.0 software. *P* value < .05 was considered significant.

**Results**: A total of nine eligible studies (5 RCTs and 4 observational studies) comprising 1851 patients were selected for the final analysis. The results of meta-analysis showed that dexmedetomidine significantly reduced the incidence of postoperative JET (OR =0.35, 95% CI: 0.22 to 0.53, *P* < .00001), but there was no significant difference between groups in AKI (OR =0.44, 95% CI: 0.19 to 1.04, *P* = .06) and all-cause mortality (OR =0.87, 95% CI: 0.35 to 2.14, *P* = .77).

**Conclusions**: The administration of perioperative dexmedetomidine effectively prevents JET in pediatric patients undergoing cardiac surgery but has no significant effect on postoperative renal function. However, the quality of evidence for these findings is low; thus, future larger scale randomized studies are needed to verify the real clinical effects of dexmedetomidine prophylaxis in pediatric patients.

**KEYWORDS**
acute kidney injury, dexmedetomidine, junctional ectopic tachycardia, meta-analysis

## 1 | INTRODUCTION

Junctional ectopic tachycardia (JET) frequently occurs in the early phase following surgical operation for congenital heart disease in pediatric patients, with an estimated incidence varying from 5.6% to 14.0%.[1-5] Within this population, JET is often associated with hemodynamic instability, longer mechanical ventilation times, increased length in the intensive care unit (ICU), and higher mortality rates. For this arrhythmia, several treatments have been employed in different pediatric centers, such as the use of beta-blockers, flecainide,

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magnesium sulfate, or hypothermia, and have been proven to be effective.[2,6,7] However, few of the current medications are ideal in preventing or reducing the occurrence of JET after pediatric cardiac surgery with the exception of amiodarone.[8]

Acute kidney injury (AKI) is also a serious complication in pediatric patients undergoing cardiac surgery with the use of cardiopulmonary bypass (CPB). The exact pathogenesis of AKI remains unclear but involves multiple pathways. Current views suggest that the complex interaction of CPB-induced inflammatory response, hemodynamic status, and nephrotoxic factors is tightly interrelated with the development of AKI.[9] Recent studies have reported the incidence of AKI of 27% to 52%, and worsening renal function was associated with increased morbidity and mortality.[10-12] Unfortunately, there are no definite strategies that have been confirmed to be effective in the prevention of CPB-associated AKI.

Dexmedetomidine is a highly selective α2 adrenoceptor agonist with sedative, analgesic, and anxiolytic properties and is widely used as a sedative and analgesic in the ICU. Currently, several small, single-center randomized controlled trials (RCTs) reported that prophylactic dexmedetomidine is useful for the prevention of JET in pediatric cardiac surgery patients.[13-16] Furthermore, the present research also suggested that the administration of dexmedetomidine might reduce the incidence of AKI after cardiac surgery with CPB.[17] However, there are few reviews that have evaluated the effects of prophylactic perioperative dexmedetomidine administration on JET and AKI in pediatric patients having undergone cardiac surgery. Therefore, we conducted a systematic literature review and meta-analysis to address this issue.

## 2 | METHODS

### 2.1 | Data source and search strategy

This systematic review was registered with PROSPERO (CRD42017083880). PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs and observational cohort studies from its inception to March 2018. The search terms were: dexmedetomidine AND (children OR pediatric) AND (tachycardia OR arrhythmias OR renal OR kidney) AND (cardiac surgery OR heart surgery). Only published articles in rigorous peer-reviewed scientific journals were included. The articles' language was restricted to English. Two independent investigators (LX and ZCX) first screened the titles and abstracts to judge whether they contained available information of interest to us. Then, the full versions of the manuscripts were downloaded from the literature databases for further evaluation.

### 2.2 | Selection criteria and endpoints

Selection criteria were as follows: (1) study designs were either RCTs or observational cohort studies; (2) participants were pediatric patients (from birth to 18 years) having undergone cardiac surgery with CPB; (3) intervention consisted of perioperative dexmedetomidine use (pre-, intra-, or immediate postoperative continuous infusion before onset of JET) and was compared with a placebo or other drugs; (4) the primary outcomes investigated were the incidence of postoperative JET or AKI (defined as KDIGO [Kidney Disease: Improving Global Outcome], RIFLE [risk, injury, failure, loss of kidney function, and end-stage kidney disease], or AKIN [acute kidney injury network]).

The primary end points of this meta-analysis were the incidence of JET and AKI after pediatric cardiac surgery, and the secondary outcome was all-cause mortality (in-hospital or within 30 days).

### 2.3 | Diagnostic criteria for JET

Diagnostic criteria included the following: (1) tachycardia with a QRS wave similar to sinus rhythm; (2) a ventricular rate more than 170 beats/min; (3) atrioventricular dissociation with or without hemodynamic compromise; (4) a ventricular rate faster than the atrial rate.

### 2.4 | Data extraction

For each study, we recorded the first author, publication year, sample size, age, and gender composition of the subjects, interventions, comparisons, and clinical parameters. Data extraction was conducted independently by LX and ZCX from the included articles that met our selection criteria. Extracted data were entered into a standardized data extraction table and checked by a third investigator (LHY). Any disagreements were resolved by discussion and consensus.

### 2.5 | Quality assessment

The methodological quality of RCTs was assessed by the Jadad scale, and the observational studies were evaluated using the Newcastle-Ottawa score (NOS). The Jadad scores ranged from 0 to 5 points and NOS ranged from 0 to 9 points. The studies were considered to be of high quality if the Jadad score was ≥3 or the NOS was ≥7. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[18,19]

### 2.6 | Statistical analysis

The meta-analysis was performed with the Review Manager software version 5.3 (Nordic Cochrane Center, The Cochrane Collaboration, 2012, Copenhagen, Denmark). For dichotomous outcomes, odds ratio (ORs) with 95% confidence intervals (CIs) were calculated and pooled using a random-effects model. The heterogeneity of the results was quantitatively evaluated with $I^2$ and chi-square tests. Studies with $I^2$ statistics of 25% to 50% suggested low heterogeneity and of 50% to 75% suggested moderate heterogeneity, and

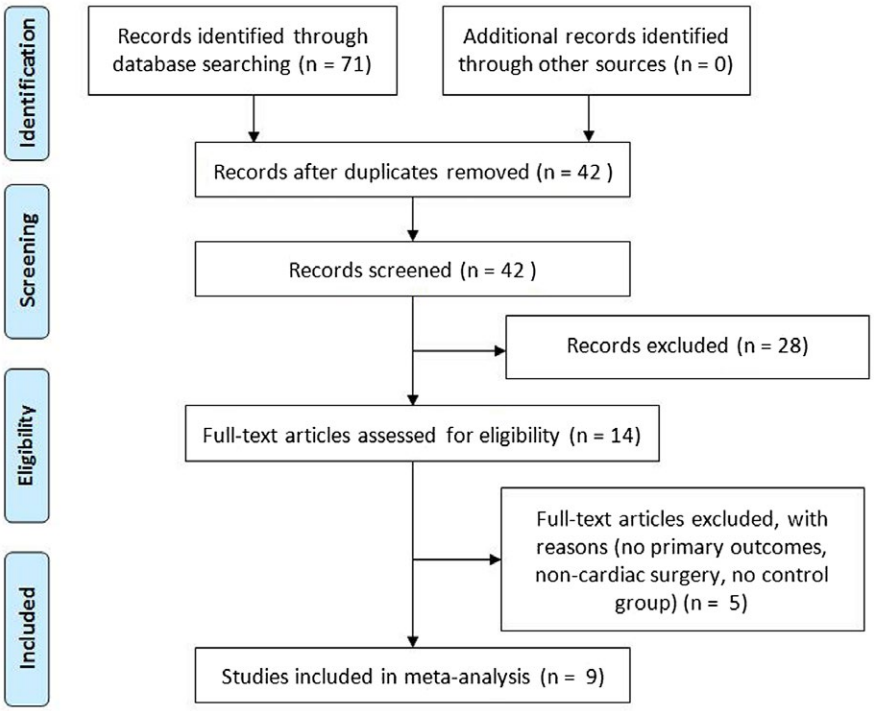


**FIGURE 1** A flow diagram for the meta-analysis

an $I^2$ of more than 75% was considered to have high heterogeneity. To ensure the credibility of the combined results in our study, we employed a sensitivity analysis by excluding outcome measures from each included study one by one. Publication bias was assessed by Begg's test using Stata software version 12.0 (StataCorp, College Station, Texas). *P* values less than .05 were considered significant.

## 3 | RESULTS

### 3.1 | Description of studies

The initial search retrieved 71 records from the major bibliographic databases (PubMed = 32, Web of Science = 30, and CENTRAL = 9). After duplicates and irrelevant articles were removed, 14 potentially suitable articles were evaluated in depth. Five studies were excluded for several reasons including the lack of primary outcomes, evaluation of noncardiac surgery, and the lack of a control group. Eventually, 9 studies comprising 4 RCTs,[13,14,16,20] 1 quasi-RCT[15] and 4 observational cohort studies[21-24] ultimately met our selection criteria and were included in the quantitative synthesis. Among them, 7 studies were pooled for JET,[13-16,21,22,24] and 2 studies were pooled for AKI.[20,23] A flow diagram for the meta-analysis is presented in Figure 1.

The main characteristics and demographics of the subjects of the included studies are presented in Tables 1 and 2. The studies were conducted in 4 countries and published from 2011 to 2017. The sample size of the included studies ranged from 29 to 936 patients, with a total of 1851 patients between the ages of 2.6 and 198 months were included in this meta-analysis. One RCT was a three-group design study, in which both dexmedetomidine and amiodarone were compared with a placebo.[14] Two investigators agreed on every item of the Jadad scale and NOS. The mean scores for the RCTs and observational studies were 3.0 and 8.8, respectively.

### 3.2 | Meta-analysis of the outcomes

In 7 studies (4 RCTs and 3 observational studies, including 8 comparisons) with 1646 participants, JET occurred in 138 (8.4%) patients (dexmedetomidine group, 45/876 [5.1%]; control group, 93/770 [12.1%]). Meta-analysis showed that the use of dexmedetomidine was associated with a reduced incidence of JET (OR = 0.35, 95% CI: 0.22 to 0.53, $z = 4.87$, $P < .00001$; chi-square = 7.97, $I^2 = 12\%$) (Figure 2). No publication bias was observed (Begg's test, $P = .71$) (Figure 3).

AKI was reported in 73 (31.3%) patients among 2 studies (1 RCT and 1 observational study) including 233 patients (dexmedetomidine group, 28/117 [23.9%]; control group, 45/116 [38.8%]). There was no significant difference in the incidence of AKI between both groups (OR =0.44, 95% CI: 0.19 to 1.04, $z = 1.87$, $P = .06$; chi-square =1.41, $I^2 = 29\%$). No publication bias was observed (Begg's test, $P = 1.0$).

All-cause mortality was reported in 5 studies (3 RCTs and 2 observational studies, including 6 comparisons) with 780 participants, and the overall death rate was 2.8% (dexmedetomidine group, 10/411 [2.4%]; control group, 10/369 [2.7%]). There was no statistically significant reduction in mortality rate due to the use of dexmedetomidine. (OR =0.87, 95% CI: 0.35 to 2.14, $z = 0.30$, $P = .77$; chi-square = 1.86, $I^2 = 0$) (Figure 4). No publication bias was observed (Begg's test, $P = .26$).

**TABLE 1** Characteristics of the included studies

| Study | Region | Design | Quality score | DEX infusion rate | Duration of intervention or control | Control | Clinical end point | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | JET | AKI | Mortality | Group |
| Chrysostomou 2011 | USA | Prospective cohort study | 9 | 0.76 ± 0.04 μg/kg/h | Start after induction and lasts for 38 ± 4 h | Fentanyl | 0 | NA | 1 | DEX |
| | | | | | | | 2 | NA | 0 | Control |
| Rajput 2014 | India | RCT | 3 | 0.5 μg/kg; 0.5 μg/kg/h | Loading dose; continuous infusion until weaning ventilator in ICU | Normal saline | 10 | NA | 0 | DEX |
| | | | | | | | 22 | NA | 0 | Control |
| Kadam 2015 | India | Quasi-RCT | 2 | 1 μg/kg; 0.75 μg/kg/h | Loading dose; before induction and lasts for 48 h | No drug | 4 | NA | 1 | DEX |
| | | | | | | | 11 | NA | 1 | Control |
| Shuplock 2015 | USA | Retrospective cohort study | 9 | 9.13 (3.88–20.2)* μg/kg | Postoperative continuous infusion for a median of 12.8 h | Normal saline | 17 | NA | NA | DEX |
| | | | | | | | 29 | NA | NA | Control |
| El-Shmaa (1) 2016 | Egypt | RCT | 2 | 1 μg/kg; 0.5 μg/kg/h | Loading dose; 10 min before induction and lasts for 72 h | Normal saline | 2 | NA | 1 | DEX |
| | | | | | | | 10 | NA | 2 | Control |
| El-Shmaa (2) 2016 | Egypt | RCT | 2 | 1 μg/kg; 0.5 μg/kg/h | Loading dose; 10 min before induction and lasts for 72 h | Amiodra-one | 2 | NA | 1 | DEX |
| | | | | | | | 2 | NA | 1 | Control |
| Kwiatkowski 2016 | USA | Retrospective cohort study | 9 | 0.5 μg/kg/h | Postoperative continuous infusion for a median of 212 h | No DEX | NA | 24 | 5 | DEX |
| | | | | | | | NA | 36 | 4 | Control |
| Amrousy 2017 | USA | RCT | 3 | 0.5 μg/kg; 0.5 μg/kg/h | Loading dose; 10 min before induction and lasts for 72 h | Normal saline | 2 | NA | NA | DEX |
| | | | | | | | 5 | NA | NA | Control |
| Gautam 2017 | USA | Retrospective cohort study | 8 | 1 μg/kg/h; 0.5-1 μg/kg/h | Before incision or after weaning from CPB; postoperative period | No DEX | 8 | NA | NA | DEX |
| | | | | | | | 12 | NA | NA | Control |
| Jo 2017 | Korea | RCT | 5 | 0.5 μg/kg; 0.5 μg/kg/h | Loading dose; 15 min before induction until the end of surgery | Normal saline | NA | 4 | NA | DEX |
| | | | | | | | NA | 9 | NA | Control |

*Notes:* Data were expressed as median value and interquartile range. Abbreviations: AKI: acute kidney injury; CPB: cardiopulmonary bypass; DEX: dexmedetomidine; ICU: intensive care unit; JET: junctional ectopic tachycardia; NA: not available; RCT: randomized controlled trial.

**TABLE 2** Summary of demographic and baseline of the included studies

| Study | Group | Patients (M/F) | Age (months) | Weight (kg) | CPB time (min) | ACC time (min) | Preoperative HR | HR while coming of CPB |
|---|---|---|---|---|---|---|---|---|
| Chrysostomou 2011 | DEX | 32 (21/34) | 4.8 (0.16–198) | 5.3 (2.6–83) | 93 ± 7 | 33 ± 6 | NA | NA |
| | Control | 20 (18/12) | 2.6 (0.13–158) | 3.9 (2.6–99) | 79 ± 9 | 30 ± 6 | NA | NA |
| Kadam 2015 | DEX | 47 (29/18) | 35.5 ± 58.3 | 11.69 ± 10.96 | NA | NA | 118.56 ± 17.937 | 137.78 ± 19.13 |
| | Control | 47 (27/20) | 28.2 ± 37.6 | 10.19 ± 6.74 | NA | NA | 126.53 ± 13.385 | 148.03 ± 18.196 |
| Rajput 2014 | DEX | 110 (86/24) | 33.2 ± 18.8 | 10.0 ± 4.12 | 85.48 ± 26.11 | 62.25 ± 22.01 | 132.39 ± 17.94 | 129.59 ± 16.35 |
| | Control | 110 (76/34) | 32.5 ± 17.3 | 10.62 ± 4.32 | 86.59 ± 19.49 | 29.59 ± 18.29 | 129.26 ± 13.05 | 149.59 ± 18.40 |
| Shuplock 2015 | DEX | 468 (239/229) | 26.1 (5.8–59.8) | NA | 94 (63–133) | 30.5 (2–56) | NA | NA |
| | Control | 468 (244/224) | 3.6 (3.6–31.9) | NA | 95 (61–130) | 33 (0–57) | NA | NA |
| El-Shmaa (1) 2016 | DEX | 30 (13/17) | 7.2 ± 4.06 | 18.4 ± 8.12 | 131.06 ± 9.11 | 91.33 ± 12.52 | 120.96 ± 7.75 | 127.83 ± 8.95 |
| | Control | 30 (18/12) | 7.43 ± 4.33 | 20.6 ± 10.71 | 130.4 ± 12.1 | 94.5 ± 12.8 | 124.0 ± 7.08 | 144.0 ± 7.08 |
| El-Shmaa (2) 2016 | DEX | 30 (13/17) | 86.4 ± 48.7 | 18.4 ± 8.12 | 131.06 ± 9.11 | 91.33 ± 12.52 | NA | 127.83 ± 8.95 |
| | Control | 30 (16/14) | 89.2 ± 52.0 | 18.86 ± 8.67 | 129.76 ± 14.61 | 97.76 ± 12.38 | NA | 133.43 ± 8.22 |
| Kwiatkowski 2016 | DEX | 102 (58/44) | 10 (4, 36) | 7 (3, 47) | 129 (77, 180) | 61 (33, 107) | NA | NA |
| | Control | 102 (58/44) | 7 (5, 13) | 7 (5, 16) | 113 (76, 190) | 56 (30, 84) | NA | NA |
| Amrousy 2017 | DEX | 60 (40/20) | 17.3 ± 4.1 | 12.4 ± 1.1 | 130.4 ± 12.1 | 94.5 ± 12.8 | 120 ± 7.4 | 130.6 ± 9 |
| | Control | 30 (18/12) | 18.3 ± 5.14 | 12.6 ± 1.7 | 132.3 ± 9.8 | 98.6 ± 9.6 | 124 ± 7.1 | 144 ± 7.1 |
| Gautam 2017 | DEX | 99 (55/44) | 10.8 (0, 181.2) | 7.6 (2.7, 86) | 83 (15, 325) | 49 (0, 87) | NA | NA |
| | Control | NA | NA | NA | NA | NA | NA | NA |
| Jo 2017 | DEX | 15 (9/6) | 31 ± 14 | 11.8 ± 2.2 | 107 ± 39 | 67 ± 34 | NA | NA |
| | Control | 14 (9/5) | 32 ± 19 | 11.3 ± 3.2 | 10.6 ± 34 | 69 ± 27 | NA | NA |

*Notes:* Data were expressed as mean value and standard deviation or median value and interquartile range unless indicated otherwise. Abbreviations ACC: aortic cross-clamp; CPB: cardiopulmonary bypass; DEX: dexmedetomidine; F: female; HR: heart rate; M: male; NA: not available.

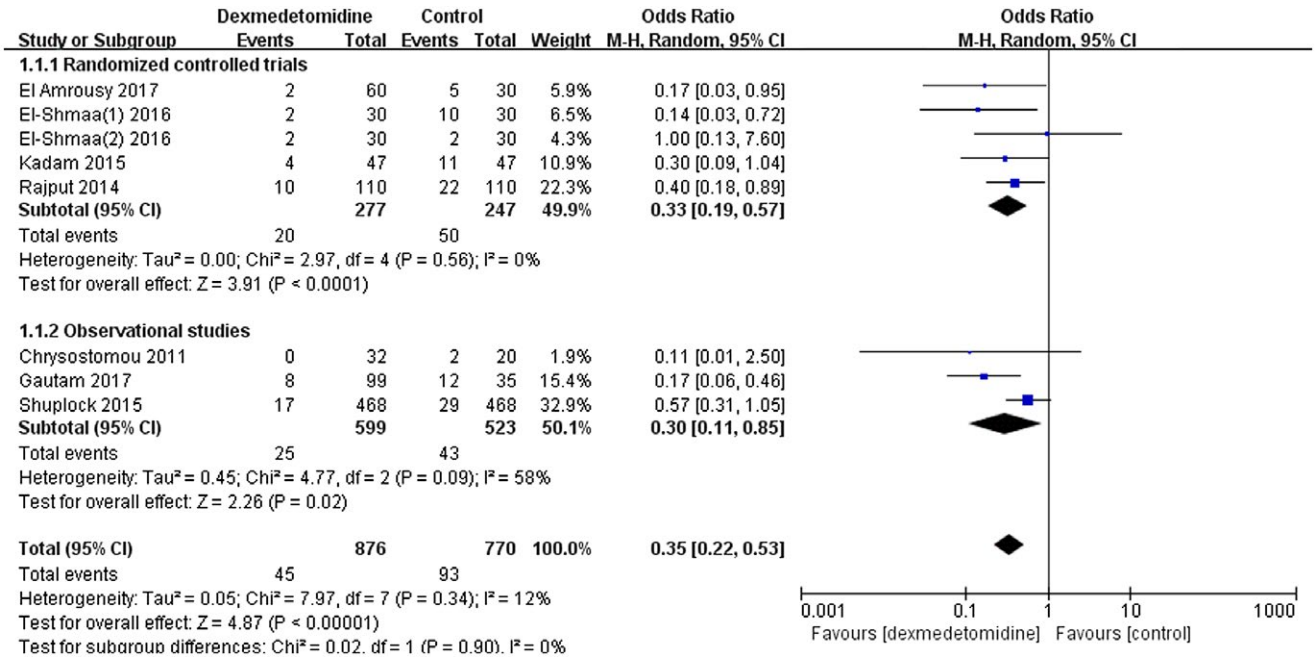


**FIGURE 2** Dexmedetomidine decreased the incidence of postoperative junctional ectopic tachycardia. Abbreviations: CI: confidence interval; M-H: Mantel-Haensel

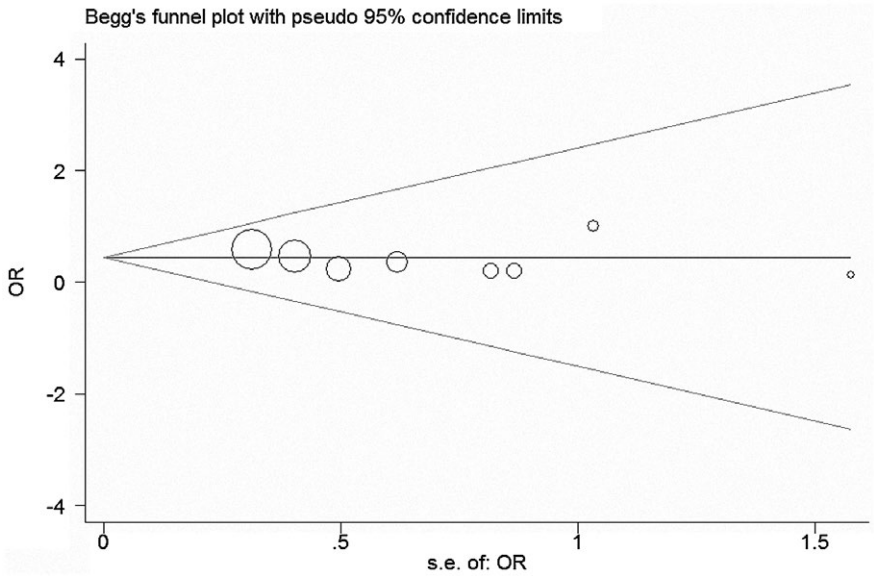


**FIGURE 3** Funnel plot of Begg's test for junctional ectopic tachycardia

Sensitivity analysis excluding each included study one by one did not significantly alter the effect estimate of JET and mortality.

## 4 | DISCUSSION

The major purpose of this meta-analysis was to evaluate whether prophylactic perioperative dexmedetomidine administration can prevent postoperative JET and AKI in pediatric patients having undergone cardiac surgery. Our analysis found that prophylactic dexmedetomidine infusion was associated with a reduced incidence of JET after pediatric surgery, while the incidence of AKI and all-cause mortality did not differ significantly between groups.

JET is a special type of supraventricular tachycardia occurring after cardiac surgery and often accompanied by hemodynamic instability and higher mortality rates. It is a life-threating condition if not treated in a timely manner. Its precise mechanism remains elusive, but it is mainly attributed to the mechanical trauma of the proximal

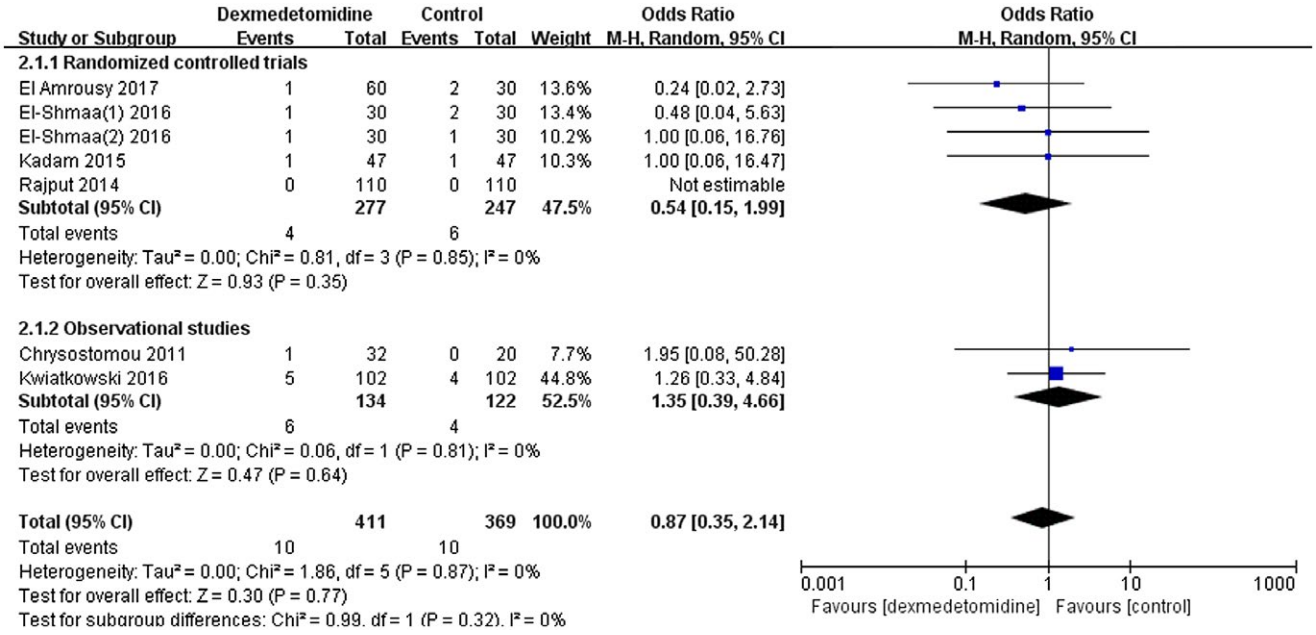


**FIGURE 4** Forest plot for all-cause mortality. Abbreviations: CI: confidence interval; M-H: Mantel-Haensel

conduction system due to suture placement or indirect stretch injury.[1] Previously reported nonsurgical risk factors for postoperative JET include being of a younger age, longer bypass and cross-clamp times, complexity of surgical operation undergone, low levels of plasma magnesium, and use of inotropic agents in the patient.[3,25-27] Several therapeutic protocols have been shown to be effective for the treatment of postoperative JET such as the use of beta-blockers, hypothermia (maintaining core temperature approximately 35°C), and magnesium sulfate,[2,6,7] but prevention of the condition is the ideal. To our knowledge, with the exception of amiodarone, there are currently few medications that can prevent or decrease the occurrence of JET after pediatric cardiac surgery.[8]

Dexmedetomidine was mainly used in the adult ICU for sedative and analgesic purposes since its approval by the US Food and Drug Administration for clinical use. Previous studies have confirmed that dexmedetomidine could decrease the release of catecholamine through stimulation of α2 adrenoreceptors, leading to sympatholytic action with accompanying negative dromotropic and chronotropic effects.[28,29] In addition, dexmedetomidine also suppresses both sinus and atrioventricular nodal functions by increasing vagal nerve activation.[30] Kamibayashi et al, suggested that these actions may also be mediated by a non–adrenergic receptor, namely an imidazoline receptor.[31] Compared with other anesthetic drugs, dexmedetomidine has obvious advantages, such as good sedative and analgesic effects and minimal respiratory depression, and is well tolerated in ventilated patients. Its main side effect is bradycardia; however, this side effect made the drug a good therapeutic option for the prevention or control of various tachyarrhythmias, such as JET after pediatric cardiac surgery.[13-16]

Our meta-analysis showed a reduced incidence of postoperative JET in association with dexmedetomidine administration. More importantly, we found that the effect of dexmedetomidine seems to be related to the timing of its administration. In 6 of the 7 included studies, dexmedetomidine was infused pre/intraoperatively and was successful in preventing tachyarrhythmias after pediatric cardiac surgery. While in a study by Shuplock et al, the administration of dexmedetomidine in the immediate postoperative period was not associated with a significant reduction of tachyarrhythmias after congenital heart surgery in children.[24] This finding indicates that dexmedetomidine is possibly more effective for the prevention of JET with pre/intraoperative administration compared with postoperative administration.

In the development of cardiac surgery associated AKI, at least six major pathways are involved including exogenous and endogenous toxins, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation, and oxidative stress.[32] To date, the exact mechanism by which dexmedetomidine plays a renoprotective role is not well understood, but anti-inflammation, sympatholytic effects, cytoprotective effects and diuresis may be the major contributors in reducing deterioration of renal function.[33,34] The latest meta-analysis with 1575 patients suggested that perioperative administration of dexmedetomidine in adults undergoing cardiac surgery may reduce the risk of postoperative AKI (OR: 0.65, 95% CI: 0.45 to 0.92, $P = .02$).[17] However, the effects of dexmedetomidine on postoperative renal function in pediatric cardiac surgery patients remained unclear.

Based on our literature review, there are two studies including 1 RCT and 1 retrospective study that have assessed the efficacy of dexmedetomidine in the prevention of pediatric cardiac surgery

associated AKI.[20,23] Positive renoprotective effects were reported in these two studies. However, in our data analysis, although the combined results with a random-effects model revealed a tendency of lower AKI incidence in dexmedetomidine-treated patients, the pooled OR failed to reach statistical significance ($P = .06$). Relatively small sample sizes may account for this result; however, a potential renoprotective role of prophylactic dexmedetomidine administration in pediatric cardiac surgery should be considered and confirmed in future larger randomized studies.

Our study has several limitations. First, the pooled raw data come from five RCTs and four observational cohort studies. Compared with the randomized trials, the observational studies were highly subject to unadjusted confounders, such as age, sex, this would affect the strength of evidence in our results. Second, the sample sizes of the included RCTs were relatively small; thus, future larger randomized trials are needed. Third, JET after pediatric cardiac surgery may have several different causes; thus, it may be inadequate to simply attribute the lower risk of postoperative JET to dexmedetomidine use. Finally, the exclusion of non-English studies may be inappropriate; however, Begg's test for JET did not display statistical significance.

In summary, the current evidence suggests that the use of prophylactic perioperaive dexmedetomidine is associated with a decreased incidence of JET in pediatric patients after cardiac surgery but has no significant effect on postoperative renal function. However, the reliability of our results might be weakened by the limited number of suitable studies and the unavoidable heterogeneity among the included studies. Thus, future high-quality, large trials are needed to verify the effect of dexmedetomidine prophylaxis in pediatric cardiac surgery patients and to ascertain the optimal time of its use.

## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

*Study design*: Xin Li, Chengxin Zhang, Shenglin Ge
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