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The effect of intraoperative dexmedetomidine on acute kidney injury after pediatric congenital heart surgery

A prospective randomized trial

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Abstract

Background: Dexmedetomidine has been reported to have a renal protective effect after adult open heart surgery. The authors hypothesized that intraoperative infusion of dexmedetomidine would attenuate the decrease in renal function after pediatric open heart surgery.

Methods: Twenty-nine pediatric patients (1–6 years) scheduled for atrial or ventricular septal defect repair were randomly assigned to receive either continuous infusion of normal saline (control group, n = 14) or dexmedetomidine (a bolus dose of 0.5 μg/kg and then an infusion of 0.5 μg/kg/h) (dexmedetomidine group, n = 15) from anesthesia induction to the end of cardiopulmonary bypass. Serum creatinine (Scr) was measured before surgery (T0), 10 minutes after anesthesia induction (T1), 5 minutes after cardiopulmonary bypass weaning (T2), 2 hours after T2 (T3), and after postoperative day 1 (POD1) and postoperative day 2 (POD2) and estimated glomerular filtration rates (eGFRs) were calculated. Renal biomarkers were measured at T1, T2, and T3. Acute kidney injury (AKI) was defined as an absolute increase in Scr of ≥ 0.3 mg/dL or a percent increase in Scr of ≥50%.

Results: The incidence of AKI during the perioperative period was significantly higher in the control group than in the dexmedetomidine group (64% [9/14] vs 27% [4/15], $P = .042$). eGFR was significantly lower in the control group than in the dexmedetomidine group at T2 (72.6 ± 15.1 vs 83.9 ± 13.5, $P = .044$) and T3 (73.4 ± 15.4 vs 86.7 ± 15.9, $P = .03$).

Conclusion: Intraoperative infusion of dexmedetomidine may reduce the incidence of AKI and suppress post-bypass eGFR decline.

Abbreviations: AKI = acute kidney injury, AKIN = acute kidney injury network, ASD = atrial septal defect, BIS = bispectral index score, CPB = cardiopulmonary bypass, CVP = central venous pressure, eGFR = estimated glomerular filtration rate, FE_{Na} = fractional excretion of sodium, HR = heart rate, IL = interleukin, KIM-1 = and kidney injury molecule-1 (KIM-1), MAP = mean arterial pressure, NGAL = neutrophil gelatinase-associated lipocalin, POD = postoperative day, RFI = renal failure index, Scr = serum creatinine, S_{Na} = serum sodium, TNF = tumor necrotic factor, U_{Alb} = urine microalbumin, Ucr = urine creatinine, U_{Na} = urine sodium, U_{NAG} = urine N-acetyl-beta-D-glucosaminidase, VSD = ventricular septal defect.

Keywords: acute kidney injury, dexmedetomidine, glomerular filtration rate, pediatric heart surgery

1. Introduction

Acute kidney injury (AKI) is common after pediatric congenital heart surgery under cardiopulmonary bypass (CPB) and may delay the recovery.[1] In a large prospective cohort study on AKI after aortic surgery, 30-day mortality was 32.5% among patients with an absolute increase in serum creatinine (Scr) of ≥0.5 mg/dL within the first 48 hours postoperatively, whereas mortality was 2.1% among those with an increase in Scr ≤0.3 mg/dL.[2] Although clinically significant deterioration of kidney function is rare in children after cardiac surgery,[3] 40% and 88% of pediatric patients experience Scr doubling and AKI as defined by the pediatric-modified RIFLE criteria (risk, injury, failure, loss of kidney function, and end-stage kidney disease) after cardiac surgery, respectively.[4] Furthermore, AKI is known to be an important independent factor of intensive care unit stay after CPB in pediatric patients.[5]

The mechanism of AKI after open heart surgery is multifactorial. Heart surgery with CPB provokes systemic inflammatory responses, which increases inflammatory cytokines, endotoxin and metabolic products.[6] It also induces ischemic reperfusion injury, oxidative stress, and neurohormonal activation.[6] In addition, surgical stress *per se* induces sympathetic activation, which leads to hemodynamic instability and renal vasoconstriction.[7]

Dexmedetomidine has been reported to provide renal protection by improving tubular architecture and function following renal ischemia.[8] In a previous clinical study in adults, it was

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suggested that perioperative infusion of dexmedetomidine might reduce the incidence and severity of AKI and intensive care unit stay after valvular heart surgery.[9]

We hypothesized that intraoperative infusion of dexmedetomidine would attenuate the decrease in renal function after pediatric open heart surgery. Accordingly, the purpose of this prospective randomized study was to investigate the effect of intraoperative dexmedetomidine infusion on kidney function after congenital heart surgery with CPB in pediatrics.

2. Methods

The institutional review board of Gachon University Gil Hospital approved this study (Ref: GCIRB 2013-163). The study was registered at ClinicalTrials.gov (NCT 01920542). Parents or legal guardians provided written informed consent for all participants.

Thirty pediatric patients (1–6 years), scheduled for repair of a congenital atrial septal defect (ASD) or a ventricular septal defect (VSD), were initially enrolled in this prospective study. Patients with a preoperative Scr of ≥0.7 mg/dL, cyanotic heart disease, any arrhythmia, patent ductus arteriosus, coarctation of the aorta, severe left ventricular dysfunction (preoperative ejection fraction of <50% by transthoracic echocardiography), signs of right heart failure, preoperative inotropic drug use, vasopressor use, active respiratory disease, or younger than 12 months were excluded. Patients were randomly divided into control group (n = 15) or dexmedetomidine group (n = 15) using a randomized list generated using Excel 2007 (Microsoft Office, Redmond, WA) without stratification.

No patient received any premedication. Anesthesia was induced with ketamine 1 to 2 mg/kg, sufentanil 1 to 2 μg/kg, and rocuronium of 0.8 mg/kg. Anesthesia was maintained with sevoflurane 2 to 3 vol%, rocuronium and sufentanil. A bispectral index score was maintained between 40 and 60 during anesthesia. Arterial catheters were inserted in the radial and femoral arteries. A right internal jugular venous catheter was inserted. A senior anesthesia trainee prepared 50 mL of normal saline for the control group or 50 mL of dexmedetomidine (4 μg/mL) for the dexmedetomidine group. From 10 minutes after anesthesia induction to CBP weaning, 0.5 μg/kg of dexmedetomidine or the same volume of normal saline was infused over 10 minutes as a bolus dose and then 0.5 μg/kg/h of dexmedetomidine[10] or the same volume of normal saline was administered as a maintenance dose in the dexmedetomidine and control groups, respectively. Anesthesiologist and pediatric intensive care providers who were blinded to the study group performed hemodynamic care and sampling of urine and blood in the operating room and intensive care unit, respectively.

When starting CPB and rewarming, sufentanil of 20 μg (body weight <10 kg) or 30 μg (body weight ≥10 kg) and midazolam of 0.2 mg/kg were administered. When needed, patients received milrinone, dopamine, or epinephrine during CPB weaning according to their condition.

According to the acute kidney injury network (AKIN) criteria, AKI was defined as an absolute increase in Scr of ≥0.3 mg/dL, a percent increase in Scr of ≥50%, or a decrease in urine output of <0.5 mL/kg/h for >6 hours.[11]

Scr was measured before surgery (T0), 10 minutes after anesthesia induction (T1), 5 minutes after CPB weaning (T2), 2 hours after T2 (T3), and after postoperative day 1 (POD1) and postoperative 2 day (POD2). Estimated glomerular filtration rate (eGFR) was calculated using Counahan-Barratt's formula[12] (eGFR [mL/min/1.73 m^2] = [0.43 × height in cm]/Scr). Serum sodium (S_{Na}), urine creatinine (Ucr), urine sodium (U_{Na}), urine N-acetyl-beta-D-glucosaminidase (U_{NAG}), and urine microalbumin (U_{Alb}) were sampled at T1, T2, and T3, and mean arterial pressure (MAP), heart rate (HR), and central venous pressure (CVP) were recorded at the same time points. U_{NAG} to Ucr ratios (U_{NAG}/Ucr) were calculated, and renal failure index (RFI) and fractional excretion of sodium (FE_{Na})[12] were calculated using the following equations: $RFI = U_{Na} \times Scr/Ucr$, and $FE_{Na} = 100 \times (U_{Na} \times Scr)/(Ucr \times S_{Na})$.

Given an AKI incidence in children after CPB of 88%[4] and assuming a reduction of 30% at an α-error of 0.05 and a ß-error of 90%, at least 15 patients were needed per the group when an expected drop out rate of 10% was included.

Statistical analysis was performed using PASW Statistics ver. 13 (SPSS Inc, Chicago, IL). Results are presented as means (standard deviations) or medians (interquartile ranges) or number of patients. Patient characteristics and perioperative clinical data in the 2 study groups were compared using an independent *t* test or Fisher exact test, as appropriate. Group comparisons of hemodynamic variables and renal biomarkers at each time point were analyzed using an independent *t* test. Changes in group hemodynamic variables and renal biomarkers over time were analyzed using repeated measures analysis of variance. Statistical significance was accepted for *P* values <.05.

3. Results

Of the 30 patients initially enrolled, 1 patient in the control group was excluded from the analysis because of a change in operative plan during operation. Accordingly, the data of 29 patients were analyzed (Fig. 1). Patient characteristics and intraoperative data are summarized in Table 1. Patient characteristics, total operative times, aortic cross clamping times, and hourly urine outputs were similar in the 2 groups. Similarly, no significant intergroup differences were observed between epinephrine, dopamine, and milrinone requirements. No diuretic was used during and after the surgery.

Hemodynamic variables were presented in Table 2. No intergroup differences in MAP, HR, or CVP were observed at any time point, and changes in MAP, HR, and CVP over time were not significantly different between 2 groups.

The renal function variables are listed in Table 3. There was no intergroup difference in RFI, FE_{Na}, U_{NAG}/Ucr, or U_{Alb}/Ucr, at any time points. The changes in RFI, FE_{Na}, U_{NAG}/Ucr, and U_{Alb}/Ucr over time were not significantly different between 2 groups (*P* = .951, .892, .892, and .672, respectively). RFI and FE_{Na} increased significantly at T3 versus T1 (*P* = .015 and .019, respectively) in the control group. U_{NAG}/Ucr increased significantly at T3 versus T1 (*P* = .042) in the dexmedetomidine group. From analysis of only the VSD patients (*n* = 26), perioperative renal indices also revealed no intergroup differences at any time points, and similar changes over time between 2 groups.

The incidence of AKI during the perioperative period was significantly higher in the control group than in the dexmedetomidine group (64% [9/14] vs 27% [4/15], *P* = .042). Among 9 AKI patients in the control group, one was an ASD patient and others were VSD patients. Among 4 AKI patients in the dexmedetomidine, all were VSD patients. However, no patient had a Scr level of >0.7 mg/dL at any blood sampling time point.

Changes in Scr and eGFR are illustrated in Figure 2. No intergroup difference in Scr was observed at any time points, and changes in Scr over time were not significantly different between 2

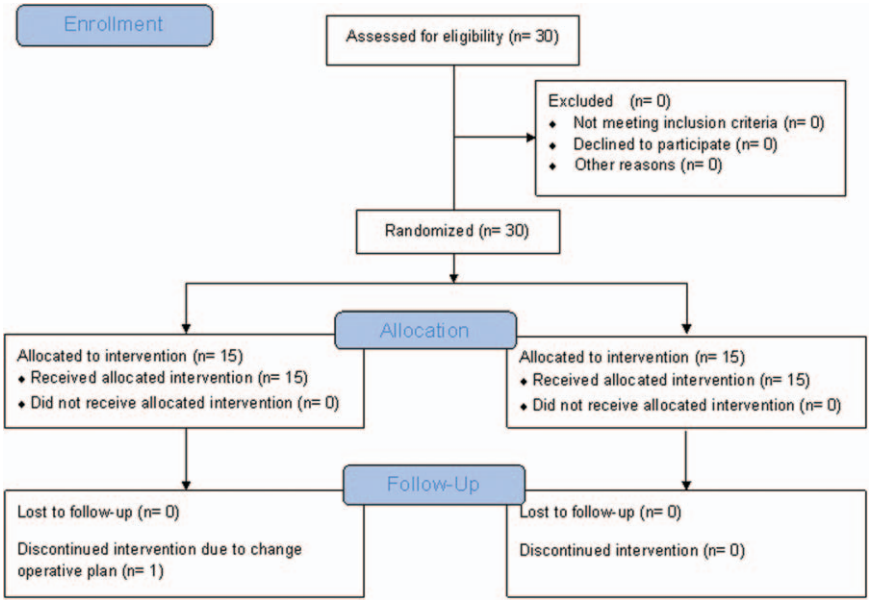

Figure 1. Patient allocation flow diagram.

groups ($P=.357$). Scr increased significantly at T2 and T3 versus T0 in both groups (all P values $<.001$). However, eGFR was significantly lower in the control group than in the dexmedetomidine group at T2 (72.6 ± 15.1 mL/min/1.73 m^2 vs 83.9 ± 13.5 mL/min/1.73 m^2, $P=.044$) and T3 (73.4 ± 15.4 mL/min/1.73 m^2 vs 86.7 ± 15.9 mL/min/1.73 m^2, $P=.03$), but changes in eGFR over time did not differ significantly between 2 groups ($P=.694$). Compared to the value at T0, eGFR decreased significantly at T2, T3, and T4 ($P<.001$, $<.001$, and .009, respectively) in the control group and at T2 and T3 (P values $<.001$) in the dexmedetomidine group. No patient received prolonged mechanical ventilation (over 24 hours) or stayed in the intensive care unit for >2 days. Furthermore, no patient required renal replacement therapy or diuretics during and after the surgery.

Table 1

Patient demographic and perioperative data.

	Control (n=14)	DEX (n=15)	*P*
Age, mo	32±19	31±14	0.878
Sex (M/F)	9/5	9/6	0.812
Weight, kg	11.1±3.2	11.8±2.2	0.483
Height, cm	85±14	88±9	0.499
Body surface area, m^2	0.50±0.11	0.53±0.07	0.394
The type of surgery (n)			
ASD/VSD	2/12	1/14	0.501
Anesthesia time, min	238±50	249±55	0.676
Operation time, min	185±46	193±45	0.725
Study drug infusion time, min	124±33	126±39	0.867
Cardiopulmonary bypass time, min	106±34	107±39	0.919
Aorta cross clamping time, min	69±27	67±34	0.911
Lowest temperature, °C	32.7±1.1	32.4±1.1	0.537
Intraoperative use of vasoactive drugs (*n*)			
Epinephrine	1	0	0.292
Dopamine	2	5	0.231
Milinone	10	9	0.518
Urine output, mL/kg/h			
During CPB	2.3±1.0	2.7±2.0	0.480
After CPB	2.6±1.8	2.3±2.0	0.678
POD1	2.9±0.9	3.0±1.2	0.860
POD2	3.8±1.2	3.0±1.3	0.127

Results are presented as mean±SD or numbers of patients. After CPB=during the 2 hours after cardiopulmonary bypass weaning, ASD=atrial septal defect, Control=patients that received intraoperative normal saline infusion, DEX=patients that received intraoperative dexmedetomidine infusion, during CPB=from anesthesia induction to cardiopulmonary bypass weaning, POD1=postoperative day 1, POD2=postoperative day 2, VSD=ventricular septal defect.

4. Discussion

This prospective, randomized trial shows that intraoperative dexmedetomidine (a loading dose of 0.5 μg/kg followed by infusion at 0.5 μg/kg/ h) may reduce the incidence of AKI and suppress post-bypass eGFR decline after pediatric congenital heart surgery under CPB. However, dexmedetomidine was not found to improve other renal biomarkers after surgery. To the best of our knowledge, this is the first prospective study to report dexmedetomidine has a renal protective effect after pediatric open cardiac surgery.

A previous multicenter trial reported that a younger age, lower body weight, lower body surface area, and prolonged CPB time are risk factors of AKI after pediatric cardiac surgery.[13] In the

Table 2

Hemodynamic variables and renal indices.

Variables	T1	T2	T3	POD 1	POD2
MAP, mmHg					
Control	65±7	60±7	82±13	86±10	82±25
DEX	64±7	63±15	72±15	83±5	78±19
HR, beats/min					
Control	119±17	121±13	143±18	125±8	133±23
DEX	114±16	119±13	129±21	128±15	132±11
CVP, mmHg					
Control	4.6±2.3	8.8±2.6	7.6±2.5	7.0±2.9	7.3±2.0
DEX	5.1±2.9	7.1±3.4	7.1±2.2	8.1±2.5	7.9±2.0

Results are presented as mean±SD or numbers of patients or medians (interquartile ranges). Control (*n*=14)=patients that received intraoperative normal saline infusion, CVP=central venous pressure, DEX (*n*=15)=patients that received intraoperative dexmedetomidine infusion, HR=heart rate, MAP=mean arterial pressure, POD1=postoperative day 1, POD2=postoperative day 2, T1=10 minutes after anesthesia induction, T2=5 minutes after cardiopulmonary bypass weaning, T3=2 hours after T2.

Table 3

Perioperative renal indices.

	Group	T1	T2	T3
RFI	Control	0.37 (0.21–0.63)	0.77 (0.32–1.02)	0.65 (0.60–1.98))*
	Dexmedetomidine	0.48 (0.30–1.20)	0.78 (0.56–1.46)	1.07 (0.52–1.57)
FE_{Na} (%)	Control	0.27 (0.15–0.47)	0.58 (0.24–0.74)	0.47 (0.43–1.38)*
	Dexmedetomidine	0.35 (0.22–0.88)	0.57 (0.41–1.09)	0.73 (0.39–1.14)
U_{NAG}/Ucr, U/g	Control	20.3 (12.4–36.9)	72.9 (27.5–459.6)	233.2 (26.8–1530.2)
	Dexmedetomidine	22.1 (8.8–42.7)	235.2 (102.6–474.1)	422.6 (128.6–1631.0)*
U_{Alb}/Ucr, mg/g	Control	18.3 (12.8–55.9)	185.4 (60.1–268.5)	34.4 (16.3–461.9)
	Dexmedetomidine	9.7 (9.1–70.1)	108.8 (17.8–441.7)	97.3 (17.7–372.2)

Values are medians (interquartile ranges). Control ($n=14$), patients that received intraoperative normal saline infusion; Dexmedetomidine ($n=15$), patients that received intraoperative dexmedetomidine infusion. FE_{Na} = fractional excretion of sodium, RFI = renal failure index, T1 = 10 minutes after anesthesia induction, T2 = 5 minutes after cardiopulmonary bypass weaning, T3 = 2 hours after T2, U_{Alb}/Ucr = U_{Alb} to Ucr ratio, U_{NAG}/Ucr = U_{NAG} to Ucr ratio.

* $P < .05$, vs T1.

present study, we only included 1- to 6-year-old patients with a simple atrial or VSD. Our patients did not have risk factors of AKI, and no patient suffered from clinically significant symptoms, signs of AKI, or needed treatment for AKI before surgery. Nonetheless, 44.8% of the patients enrolled experienced AKI fulfilling the AKIN criteria.[11] We also found renal function declined after weaning from CPB based on eGFR, RFI, FENa, and U_{NAG}/Ucr ratio results, which suggests that post-bypass renal function decline is common even in low risk patients after pediatric cardiac surgery.

Dexmedetomidine is a highly selective α_2-adreno-receptor agonist, which inhibits sympathetic outflow in the central nervous system and reduces norepinephrine release in presynaptic α_2-receptor.[14] These sympatholytic activities of dexmedetomidine might help to prevent hemodynamic variations induced by sympathetic activation after cardiac surgery.[15] Furthermore, inhibition of circulating epinephrine and norepinephrine release by dexmedetomidine might protect renal function and stabilize hemodynamic profiles. A previous animal study revealed that α_2-adrenoreceptor is widely distributed in the renal cortex and dexmedetomidine dose-dependently inhibits stimulation-evoked norepinephrine release and induces renal vasodilation.[16] Although no significant intergroup differences were observed between hemodynamic changes, in the present study, MAP, HR, and CVP were more stable in the dexmedetomidine group than in the control group after weaning from CPB. A previous study also has reported that a low bolus dose of dexmedetomidine (0.25 or 0.5 μg) had limited hemodynamic effects in health human volunteers.[17]

During CPB, contact between blood and extracorporeal circuit produces systemic inflammatory responses, the releases of various cytokines, and the activation of inflammatory cells, which can lead to kidney dysfunction.[18,19] Furthermore, an *in vitro* study demonstrated that acute inflammatory responses, as determined by the release of interleukin (IL)-8, after CPB were greater in pediatrics than in adults.[20] Other studies also demonstrated elevated serum IL-6 and -10 in children who develop AKI after cardiac surgery.[21] Although the mechanisms responsible for the effect of dexmedetomidine on renal function after CPB weaning are unclear, dexmedetomidine-induced α_2-receptor activation might suppress the production of monocytic cytokines.[22] An earlier clinical study demonstrated that intraoperative dexmedetomidine infusion significantly decreased the productions of IL-1β, tumor necrotic factor-α, and IL-10, and reduced postoperative leukocyte counts and C-reactive protein levels.[23] Another possible mechanism is that dexmedetomidine suppresses systemic inflammation via a cholinergic anti-inflammatory pathway. In a previous in-vitro study conducted using a lipopolysaccharide-induced endotoxemia model, it was suggested that the preemptive administration of dexmedetomidine might inhibit inflammatory cytokine release by modulating the vagus nerve and an α7nAChR-mediated cholinergic anti-inflammatory pathway.[24] In this present study, we observed that eGFRs were significantly higher in the dexmedetomidine group, which concurs with the results of adult studies.[9,25] In addition, a retrospective study also reported that the use of dexmedetomidine was associated with reduced AKI

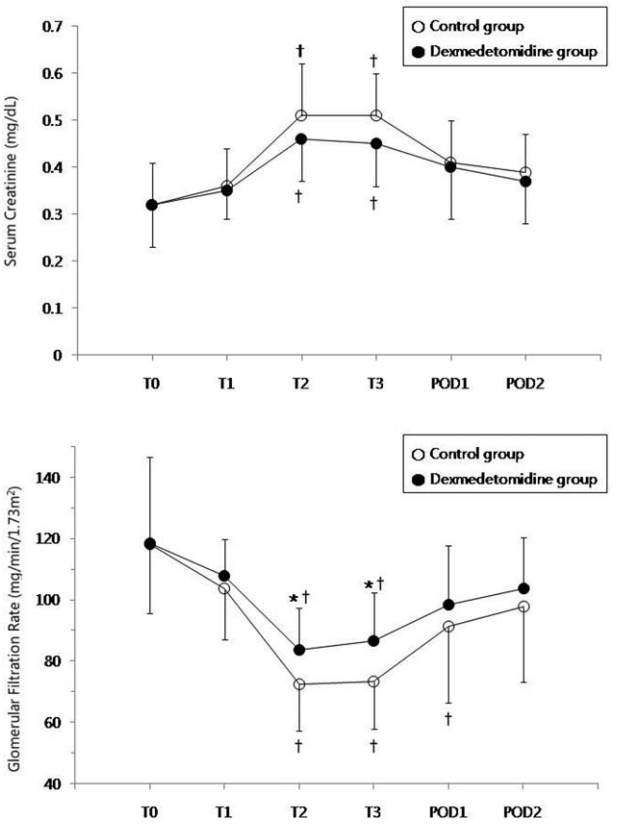

Figure 2. Perioperative changes in serum creatinine and estimated glomerular filtration rate in patients that received normal saline (the control group, ○) or dexmedetomidine (the dexmedetomidine group, ●). Error bars represent standard deviations. POD1 = postoperative day 1, POD2 = postoperative day 2, T0 = before surgery, T1 = 10 minutes after anesthesia induction, T2 = 5 minutes after cardiopulmonary bypass weaning, T3 = 2 hours after T2. * $P < .05$, vs the control group, † $P < .05$ vs T0.

incidence after pediatric congenital heart surgery.[26] Thus, it is assumed that the perioperative use of dexmedetomidine have protective effect on renal function after open heart surgery.

As the primary target for AKI management is the prevention, its early detection is very important after pediatric open heart surgery. Noninvasive biomarkers for early detection of AKI are suggested such as U_{NAG}, U_{Alb}, IL-18, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). An earlier study has reported that U_{Alb}/Ucr was a reliable predictor for AKI and its optimal cutoff value was >400 mg/g in pediatric open heart surgery.[27] In this present study, U_{NAG}/Ucr and U_{Alb}/Ucr were measured for detecting early AKI or renal tubular injury and there were no intergroup differences at any time points. Also, the number of patients with U_{Alb}/Ucr >400 mg/g at 2 hours after CPB was comparable between the control and dexmedetomidine groups (29% [4/14] vs 20% [3/15], $P = .681$) in this present study.

The present study has several limitations. First, U_{NAG}/Ucr and U_{Alb}/Ucr was measured as renal biomarkers to detect AKI, but the range of these biomarkers was too wide to detect intergroup differences. Although changes in serum and urinary biomarkers revealed a decline in renal function in both groups, the beneficial effect of dexmedetomidine on renal function was only reflected with eGFR. The change in Scr levels was also similar between the groups because it is not the most accurate marker of kidney injury, especially during the acute phase. The use of more sensitive biomarkers such as serum cystatin C or NGAL would have given better assessment of renal function in early postoperative period,[28] but Scr remains criterion standard for diagnosing the AKI and reliable predictor of AKI even immediate after cardiac surgery.[29] Second, the lack of inflammatory cytokines makes impossible to elucidate the mechanism underlying renal protective effect of dexmedetomidine. Third, the inclusion of different risk index category patients in this study. Risk-adjusted Congenital Heart Surgery Score (RACHS) indicates that secundum ASD is category 1 and VSD is category 2, and Li et al[13] have reported that no patients from the RACHS-1 category 1 surgeries developed AKI. However, only 3 ASD patients were included in this study (2 in the control and 1 in the dexmedetomidine group) and when data of only VSD patients were analyzed, the results were the same. Lastly, although calculated, the sample size is too small to extrapolate to pediatric patients with various congenital heart diseases. Larger sample size is needed for generalized results with greater precision and power. We added these comments in the discussion section.

In conclusion, intraoperative dexmedetomidine infusion may reduce the incidence of AKI and the incidence of post-bypass eGFR decline after pediatric congenital heart surgery under CPB. However, intraoperative dexmedetomidine infusion was not found to improve renal biomarkers, such as U_{NAG} and U_{Alb}, after pediatric open heart surgery.

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