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Effects of intraoperative dexmedetomidine on the incidence of acute kidney injury in pediatric cardiac surgery patients: a randomized controlled trial

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김 은 희

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Abstract

Effects of intraoperative dexmedetomidine on the incidence of acute kidney injury in pediatric cardiac surgery patients: a randomized controlled trial

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Importance: Perioperative use of dexmedetomidine, an alpha 2-adrenoreceptor agonist, reduces the incidence of postoperative acute kidney injury after adult cardiac surgery. However, large-scale randomized controlled trials of dexmedetomidine are lacking in pediatric patients.

Objective: We evaluated the incidence of AKI and the pharmacokinetics of dexmedetomidine in cardiac surgery with cardiopulmonary bypass (CPB) in pediatric patients.

Design, Setting, and Participants: We included 141 children under 7 years old, except neonates and randomly assigned them to dexmedetomidine or control groups. After anesthetic induction, in the dexmedetomidine group were administered 1 μg/kg of dexmedetomidine over 10 minutes, and an additional 0.5 μg/kg of dexmedetomidine was administered every hour during surgery. Finally, 1 μg/kg of dexmedetomidine was infused immediately after cardiopulmonary bypass was initiated. Population pharmacokinetic analysis was performed with NONMEM VII level 4 software. The covariates analyzed were age, body weight, lean body mass, presence of CPB and CPB prime volume.

Main Outcomes and Measures: The incidence of AKI defined as the Kidney Disease Improving Global Outcomes guidelines were evaluated. The effect of CPB on the pharmacokinetics of dexmedetomidine was characterized by the using the estimated pharmacokinetic parameters.

Results: The final analysis included 139 patients. The incidence of AKI did not differ between dexmedetomidine and control groups (16.9% vs. 23.5%; odds ratio 0.661; 95% CI 0.285 to 1.525; p = 0.339). Postoperative creatinine levels were lower (mean difference [95% CI]; -0.03 mg/dl [-0.05 to -0.00 mg/dl], p = 0.022), and the postoperative estimated glomerular filtration rate (mean difference [95% CI]; 10.7 ml/min/1.73m^2 [1.4 to 20.0 ml/min/1.73m^2]; p = 0.023), and intraoperative urine output (mean difference [95% CI]; 4.9 ml/kg/h [3.1 to 6.7 ml/kg/h], p = 0.001) were higher in the dexmedetomidine than control group. The incidence of arrhythmia, mechanical ventilation duration, length of stay in the intensive care unit, and hospitalization were not different between the two groups. A Two-compartment mammillary model best described the pharmacokinetics of dexmedetomidine in pediatric patients under CPB. The central volume of distribution was markedly increased from 5.92(weight 10^{-1})$^{0.641}$ L for off-CPB state and 19.4(weight 10^{-1})$^{0.641}$ L for CPB state. Meanwhile, clearance was not influenced by presence of CPB. At a simulation in a hypothetical child, the decrease of plasma concentration during CPB was not prominent

Conclusions and Relevance: The intraoperative dexmedetomidine did not reduce the overall incidence of AKI in pediatric cardiac surgery patients. In addition, we can use dexmedetomidine without adjustment of dosage or addition of a loading dose at the beginning of CPB.

Keywords: Acute kidney injury, Cardiac surgery, Dexmedetomidine, Pediatrics

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1 Introduction

Acute kidney injury after pediatric cardiac surgery increases the risk of postoperative morbidity and mortality, and the incidence of AKI has been reported to be as high as 30-50% in pediatric cardiac surgery patients (1, 2).

The pathophysiology of AKI is variable and includes hemodynamic compromise during surgery, hypovolemia, ischemic-reperfusion injury, and cardiopulmonary bypass (CPB)-induced inflammatory responses. In addition, age (patients who are <12 months old), surgical complexity, CPB duration, preoperative hypoalbuminemia, and pulmonary hypertension are also risk factors that are associated with the development of AKI (3, 4). Several studies have suggested that reducing blood transfusion, avoiding nephrotoxic agents, reducing CPB duration, and using crystalloid fluids (rather than colloid fluids) may reduce AKI during cardiac surgery (5, 6). However, the optimal method for reducing AKI during cardiac surgery is still unknown.

Recent studies have focused on the ability of a number of pharmacological interventions to reduce AKI. Results from these studies demonstrated that the incidence of postoperative renal dysfunction in adults was considerably reduced following treatment with B-type natriuretic peptide, dexmedetomidine, levosimendan, and N-acetyl cysteine, compared with the incidence of renal dysfunction in adults who received placebo (7). Among them, dexmedetomidine

has recently received attention. Perioperative dexmedetomidine reduced the incidence and severity of acute kidney injury following valvular heart surgery in adults (8). Furthermore, studies that included pediatric patients revealed that dexmedetomidine effectively reduced AKI after cardiac surgery (9-13).

However, a large scale, randomized controlled trial is still required to determine the clinical application of dexmedetomidine for pediatric cardiac surgery patients. Furthermore, plasma concentration and pharmacokinetics model of dexmedetomidine associated with AKI have not been validated.

In this study, we investigated if the continuous infusion of intraoperative dexmedetomidine was associated with a reduced risk of postoperative AKI in pediatric patients undergoing cardiac surgery and aimed to establish the pharmacokinetics model of dexmedetomidine in pediatric patient with CPB to provide proper dosing regimen of dexmedetomidine.

2 Materials and Methods

2.1 Ethics

The institutional review board (IRB) of Seoul National University Hospital (H1608-052-784, Chairperson; Park Byung-joo) approved this prospective study. We registered this study at Clinicaltrials.gov (NCT02888275; August 30, 2016). On the day before each surgery, one of the investigators reviewed the protocol of this study and obtained written informed consent from each patient's parents.

2.2 Study protocol

2.2.1 Intervention

The patients were randomly assigned to the dexmedetomidine or control groups at a 1:1 ratio. Patients were eligible for participation if they were less than seven years of age, had an American Society of Anesthesiologists physical status of 1 to 3, were assigned to risk adjustment for congenital heart surgery (RACHS) categories 2 or 3, and were undergoing cardiac surgery with CPB (14). Neonates; patients with preoperative creatinine values exceeding 1.5 mg/dl; patients with a history of renal replacement therapy, diabetes mellitus, or allergies; and patients with substantially

elevated levels of aspartate transaminase >100 units/L or alanine aminotransferase > 100 units/L were excluded.

Patients in the dexmedetomidine group were administered 1 μg/kg of dexmedetomidine over a period 10 minutes after the induction of anesthesia. An additional dexmedetomidine was administered by continuous infusion of 0.5 μg/kg/h during surgery, and 1 μg/kg of dexmedetomidine was infused immediately after CPB was initiated. Patients in the control group were administered equal amounts of normal saline at the same time points.

Anesthesia was induced with atropine (0.02 mg/kg), thiopental sodium (5 mg/kg), and fentanyl (2-3 μg/kg) and maintained with sevoflurane 2-3 vol % and a continuous infusion of remifentanil (0.2 μg/kg/min). Rocuronium (1 mg/kg) was infused continuously during the surgery to facilitate tracheal intubation. Transfusion of red blood cells, fresh frozen plasma, and platelets were managed as our institutional protocol. We maintained hemoglobin levels of > 8 g/dl in non-cyanotic children and > 10 g/dl in cyanotic children. Fresh frozen plasma or platelet concentrates were administered on the basis of rotational thromboelastometry (ROTEM, TEM International GmbH, Munich, Germany); a fibrinogen test (FIBTEM) and external test (EXTEM) were used to obtain data after protamine administration.

2.2.2 Outcomes

2.2.2.1 Primary outcome

The primary outcome was the incidence of AKI, which was determined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (15). The definition from the international KIDIGO guideline merged Risk, Injury, Failure, Loss, and End-stage renal disease and the AKI Network. This guideline has been consistently used to define AKI stage in many studies (16, 17). The incidence of AKI was measured on postoperative days 1 through 7.

The KDIGO classifies AKI into three stages: stage 1, a 0.3 mg/dl increase in plasma creatinine levels or plasma creatinine levels are 1.5 – 1.9 times higher than baseline plasma creatinine levels; stage 2, plasma creatinine levels are 2.0-2.9 times higher than baseline plasma creatinine levels; and stage 3, plasma creatinine levels are 3.0 times higher than baseline creatinine levels, an increase in serum creatinine levels to >4.0 mg/dl , initiation of renal replacement therapy, or an eGFR <35 ml /min /1.73 m^2.

2.2.2.2 Secondary outcomes

Secondary outcome measures were pharmacokinetics of dexmedetomidine; serum creatinine levels; estimated glomerular filtration rate eGFR=[k× height]/ serum creatinine (k = 0.45 for infants, k = 0.55 for all other children (18)); postoperative urine output for seven days; serum lactate levels, hemodynamic variables during infusion; perioperative fluid and transfusion requirements; a large amount of red blood cell transfusion (more than the upper quartile); vasoactive inotropic scores (VIS; [dopamine dose (μg/kg/min)] + [dobutamine dose (μg/kg/min)] + [epinephrine dose × 100 (μg/kg/min)] + [milrinone dose × 10 (μg/kg/min)] + [vasopressin dose × 10 000 (U/kg/min)] + [norepinephrine dose × 100 (μg/kg/min)]); perioperative arrhythmia; postoperative mechanical ventilation duration; intensive care unit stay and hospitalization.

Normal creatinine concentration and eGFR changes enormously with age (18-20). We therefore compared perioperative eGFR with that expected for age (average and range, 1-6 months, 77 and 39 to114 ml/min/1.73 m^2; 6-12 month, 103 and 49 to 157 ml/min/1.73 m^2; 12-24 months, 127 and 62 to 191 ml/min/1.73 m^2; 2-12 years, 127 and 89 to 165 ml/min/1.73 m^2) (21).

2.2.3 Sample size calculation

We calculated the sample size based on a 40.8% incidence of AKI after pediatric cardiac surgery at our institution. We assumed that dexmedetomidine would reduce the incidence of AKI by 50%. Using an alpha error of 5% and a beta error of 80%, the sample size was 68 patients per group. Considering the attribution rate of 10%, a total of 144 pediatric patients were required for this study.

2.2.4 Randomization and blinding

For grouping, we used a stratified randomization assignment based on RACHS criteria. A researcher independent to the study managed and concealed the randomization process and assigned the pediatric patients to each group. A research assistant nurse prepared 1 μg/ml of dexmedetomidine hydrochloride (Precedex, 100 mcg/ml, Pfizer Canada Inc., Kirkland, Canada) in a 50-ml syringe. The same amount of normal saline was prepared in a 50 ml syringe for the control group. Group assignment was blinded to participants, care providers, and those assessing the outcomes.

2.2.5 Blood sampling and assays

Three-milliliters of arterial blood was sampled into ethylene-diamine-tetra-acetic acid (EDTA) immediately after induction, and at 0, 5, 10, and 20 min after the first intravenous bolus of dexmedetomidine, Samples were also collected at 0, 5, 10, 20, 30, 40, and 60 min after the initiation of CPB, at 30 and 60 min after the termination of CPB, and at the end of dexmedetomidine infusion.

All samples were centrifuged for 10 min at 3000 rpm and stored at −70°C until assay. Plasma concentrations of dexmedetomidine were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) after liquid-liquid extraction with methyl *tertiary* butyl ether (MTBE). 200 μL of human plasma was mixed with 50 μL of internal standard (IS, 50 ng/mL, tolazoline) and 100 μL of 5 N ammonium hydroxide, then extracted with 1 mL of MTBE. Tolazoline was purchased from Toronto Research Chemicals Inc. (Toronto, Canada). Plasma samples were vortex mixed, centrifuged, and then the organic phase was evaporated to dryness at room temperature a stream of nitrogen. The residue was reconstituted in 75 μL of 50% methanol in 0.1% formic acid and injected into the LC-MS/MS system. The analyte and IS were separated on a Luna 3u CN, 100 A (100 x 2.1 mm, 3 um, Phenomenex, USA) under isocratic condition. The mobile

phases consisted of 100% water in 0.1% formic acid and 100% acetonitrile in 0.1% formic acid. Positive electrospray ionization in multiple reaction monitoring (MRM) mode was employed. The MRM was based on m/z transition of 201.14>94.82 for dexmedetomidine and 161.10>90.75 for internal standard. The calibration curve was linear over the range of 0.005 - 2 ng mL^{-1} with the coefficients of correlation (r) greater than 0.99 for all instances. The lower limit of quantification of dexmedetomidine was 0.005 ng mL^{-1}. The within-run precision and accuracy of the quality control samples (0.005, 0.015, 0.15 and 1.5 ng mL^{-1}) were less than 10.04% and 96.3%. The between-run precision and accuracy of the quality control samples were less than 8.89% and 95.4%.

2.2.6 Population pharmacokinetic analysis

Population pharmacokinetic analysis was performed with NONMEM VII level 4 (ICON Development Solutions, Ellicott City, MD, USA). Measured plasma concentrations of dexmedetomidine were fitted to one-, two-, or three compartment mammillary models using the ADVAN 13 subroutines and first-order conditional estimation with interaction. Inter-individual random variabilities of pharmacokinetic parameters were estimated assuming a log-normal distribution. Diagonal matrices were estimated for the various distributions of η, where η represents inter-individual random variability with a mean of zero and variance of ω^2. Constant coefficients of variation and combined additive and constant coefficient of variation residual error models were evaluated during the model building process. NONMEM computed the minimum objective function value (OFV), a statistical equivalent to the −2 log likelihood of the model. An α level of 0.05, which corresponds to a reduction in the OFV of 3.84 (chi-square distribution, degree of freedom = 1, $p < 0.05$), was used to distinguish between hierarchical models (22). The covariates analyzed were age, body weight, lean body mass (23), whether to implement cardiopulmonary bypass (CPB, 0 = no implementation, 1 = implementation), CPB prime volume, estimated glomerular filtration rate. The possible covariates were

first searched by plotting the relationship between the covariate candidates and the empirical Bayes *post hoc* estimates for all pharmacokinetic parameters. An allometric expression of body weight was applied to all pharmacokinetic parameters. Allometry, which addresses the relationship of body size to shape, anatomy, physiology, and behavior, might facilitate the development of a model that could be useful for children (24). Where θ_i is pharmacokinetic parameter in the i^{th} individual with body weight WT_i, θ_p is the pharmacokinetic parameter in a standardized child with a bodyweight of 10 kg; and k is scaling exponent for volumes and clearances. Non-parametric bootstrap analysis served to validate the models internally (fit4NM 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh; http://cran.r-project.org/web/packages/fit4NM/index.html; last accessed: March 16, 2011) (25). Predictive checks were also performed using fit4NM 3.3.3 (26). Deterministic simulations were performed to characterize the effect of CPB on the pharmacokinetic of dexmedetomidine by using the estimated pharmacokinetic parameters of the final model.

$$\theta_i = \theta_p \times \left(\frac{WT_i}{10} \right)^k \qquad (1)$$

2.2.7 Statistical methods

The Kolmogorov–Smirnov test was used to evaluate the normality of the data. The chi-squared test was used to compare categorical data. Student's t-test or the Mann–Whitney U test were used to compare continuous data. A mixed-effects ANOVA was performed to compare hemodynamic variables during dexmedetomidine/saline infusion over time between the control and dexmedetomidine groups. We analyzed the incidence of AKI according to diagnosis (VSD or not) and CPB duration (more than 180 min or not). For all analyses, $P < 0.05$ was considered statistically significant. MedCalc version 18.11.3 (MedCalc, Mariakerke, Belgium), SPSS version 23.0 (IBM Corporation, Armonk, NY, USA), R (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat version 3.5 for Windows (Systat Software, Inc., San Jose, CA, USA) were used for statistical analysis.

3 Results

The first participant was registered on October 12, 2016 and the last follow-up appointments were on February 15, 2018. Overall, 71 participants were included in the dexmedetomidine group, and seventy participants were included in the control group (Figure 1). Table 1 presents the demographic and clinical characteristics of each group at baseline. There were no significant differences in demographic and clinical characteristics, preoperative laboratory data, anesthesia time, CPB time, and aorta cross clamping time between the groups.

3.1 Incidence of AKI

The incidence of AKI defined by the KDIGO guidelines was not different between the dexmedetomidine group (16.9%) and the control group (23.5%; odds ratio [95% CI]: 0.661, [0.285 to 1.525]). The incidence of high-grade AKI was 7.0% in the dexmedetomidine group and 13.2% in the control group. (odds ratio [95% CI], 0.496, [0.157 to 1.565]; p = 0.23). Additionally, there were no significant differences in total mechanical ventilation duration; length of stay in the intensive care unit; hospitalization; and the rate of complications, including arrhythmia, re-sternotomy for bleeding control, and re-intubation, between the two groups (Table 2). Subgroup analysis according to the diagnosis and CPB duration showed that the incidence of AKI was not differ between groups (Table

3).

Immediate postoperative creatinine was lower (mean difference [95% CI]: -0.03 [-0.05 to -0.00]; p = 0.02), and immediate postoperative eGFR was higher (mean difference [95% CI]: 10.7 [1.4 to 20.0]; p = 0.02) in the dexmedetomidine group than those of the control group. However, considering age related normal range eGFR values, only 6 patients in the control group, and 5 patients in the dexmedetomidine group showed abnormal values from preoperative to postoperative 1 to 7 days. Incidence of abnormal eGFR values was not different between groups (P = 0.96). Also, the postoperative eGFR, creatinine, and urine output but, found no differences between the two groups. The intraoperative urine output was higher in the dexmedetomidine group than the control group (mean difference [95% CI]: 4.9 [3.1 to 6.7]; p < 0.01). (Table 4 and Figure 2).

Ten patients (14.1%) in the dexmedetomidine group, and 5 patients (7.4%) in the control group had single ventricular physiology (P = 0.31). Of those, 2 patients developed AKI (13.3 %). Incidence of AKI did not differ between single ventricular and biventricular physiology (P = 0.31).

Intraoperative red blood cell transfusion was not different between dexmedetomidine and control groups (p = 0.16). The median [IQR] of transfused red blood cell volume was 13.2 [8.2-20.8] ml/kg in all patients. Incidence of a large amount of red blood cell transfusion (more than 20ml/kg,

cutoff point of the upper quartile) was not different between groups (17 patients in dexmedetomidine group, 21 patients in control group, P = 0.46). However, patients receiving large amounts of red blood cell transfusion showed higher AKI incidence compared to others ($p < 0.01$, Odds ratio 5.39, 95% CI 2.23 to 13.03).

Heart rate was reduced during loading infusion until 20 minutes after initiation of infusion in the dexmedetomidine group compared with control group. There was significant group and time interaction (main effect of group, $p < 0.01$; main effect of time $p < 0.01$; effect of the interaction, $p < 0.01$). However, there were no differences in mean arterial pressure during initial loading and CPB loading between the two groups ($p = 0.48$ for initial loading; $p = 0.84$ for CPB loading) (Figure 3).

Post-CPB ROTEM variables showed that the EXTEM clotting time ($p = 0.010$, mean difference [95% CI]; 8.4 [1.4 to 15.5]), clot firmness time ($p = 0.024$, mean difference [95% CI]; 29.3 [3.7 to 55.0]) were prolonged and EXTEM alpha angle ($p = 0.045$, mean difference [95% CI]; -2.72 [-5.39 to -0.05]), A10 ($p = 0.019$, mean difference [95% CI]; -2.79 [-5.14 to -0.46]), A20 ($p = 0.011$, mean difference [95% CI]; -2.93 [-5.21 to -0.65]), maximal clot firmness MCF ($p = 0.005$, mean difference [95% CI]; -3.4 [-5.9 to -1.0]) were decreased in the dexmedetomidine group compared with control group. FIBTEM values were similar between the groups (Table 5).

3.2 Pharmacokinetics of dexmedetomidine

Of the 30 patients enrolled, one was excluded from the analysis because of sampling error (n = 1). We obtained 376 blood samples from 29 children. Patients' mean age, weight, and CPB time were 20.3 (19.3) months, 9.7 (4.1) kg, and 134.7 (65.1) minutes. Individual dexmedetomidine concentration plot are shown in Figure 4 and Figure 5.

Time courses of measured plasma concentration of dexmedetomidine are shown in Figure 6A and 6B. Because two loading infusions were administered, two peaks per person were observed and the concentration range was 0.081–3.668 ng/ml. Mean plasma concentration of dexmedetomidine before and after the CPB were 0.611 (0.531) ng/ml and 0.570 (0.684) ng/ml, respectively. Parameter estimates of the competing base and covariate pharmacokinetic models of dexmedetomidine are described in Table 6.

A two-compartment mammillary model best described the pharmacokinetics of dexmedetomidine in pediatric patients undergoing congenital heart surgery. CPB was a significant covariate for the central volume of distribution (V_1) (equation 2, and resulted in improvement in the OFV (43.83, $p < 0.01$, degree of freedom (27) = 1), compared to the basic model (number of model parameters = 9).

$$V_1 = 5.92 \times (1 - \text{CPB}) + 19.4 \times \text{CPB} \quad (11)$$

Application of the body weight to allometric scaling lead to a lower objective function value (ΔOFV=29.39).

Table 7 shows the population pharmacokinetic parameter estimates and results of non-parametric bootstrap replicates of the final pharmacokinetic model of dexmedetomidine. Goodness-of-fit plots of the final pharmacokinetic model for dexmedetomidine showed no trends in these fit plots (Figure 7). No trends were observed in these fit plots.

Predictive checks of the final pharmacokinetic model are presented in Figure 6C and 6D. In total, 8.9% of the data were distributed outside of the 90% prediction intervals of the predictive check. Simulated time course of plasma concentration of dexmedetomidine after administration of a loading dexmedetomidine infusion of 1 μg/kg for 10 min followed by continuous infusion at a rate of 0.5 μg/kg/h during 290 min in a hypothetical child weighing 10 kg are presented in Figure 8. The decrease of plasma concentration during CPB was not prominent.

Tables

Table 1 Patients' characteristics

	Dexmedetomidine group (n=71)	Control group (n=68)
Age (months)	18.9 (18.7)	20.9 (22.7)
Height (cm)	77.3 (16.6)	78.9 (20.5)
Weight (kg)	9.8 (4.4)	10.3 (5.5)
No. (%) Sex, male	47 (66.1)	40 (58.8)
No. RACHS category		
1	0	0
2	37	35
3	34	33
4	0	0
5	0	0
No. Operation		
VSD patch closure	31	32
TOF total correction	9	8
COA correction	0	1
Tricuspid valve repair	2	3
Mitral valve repair	4	6
Fontan operation	5	2
Rastelli operation	9	4
BCPS	4	1
BT shunt	1	0
PVR	1	2
TAPVR	0	1
Others	5	8
No. (%) Redo-sternotomy	24 (33.8)	16 (22.5)
No. (%) Pulmonary hypertension (preoperative	18 (25.3)	19 (27.9)

TTE)		
No. (%) Pre-operative diuretics	23 (32.3)	29 (42.6)
No. (%) Intraoperative diuretics	39 (54.9)	40 (58.8)
No. (%) Postoperative diuretics	21 (29.5)	23 (33.8)
Anesthesia time (min.)	331.1 (94.5)	333.8 (78.3)
Operation time (min.)	280.1 (93.6)	277.3 (75.9)
CPB time (min.)	147.8 (64.2)	142.4 (53.7)
ACC time (min.)	89.3 (46.2)	86.3 (39.5)
No. (%) CPB more than 2 times	4 (5.6)	3 (4.4)
Intraoperative maximal VIS	14.1 (4.3)	13.6 (3.7)

Data shown as absolute value and mean (SD], Risk adjustment for congenital heart surgery; RACHS, VSD; ventricular septal defect, ASD; Atrial septal defect, COA; coarctation of aorta, BCPS; bicarbopulmonary shunt, BT shunt; Blalock-taussig shunt, PVR; pulmonary valve replacement, TAPVR; total anomalous pulmonary venous return, TTE; Transthoracic echocardiography, CPB; cardiopulmonary bypass, ACC; Aorta cross clamping, VIS; vasoactive inotropics score

Table 2 Postoperative variables in the dexmedetomidine and control group

	Dexmedetomidine group (n=71)	Control group (n=68)
Incidence of Acute Kidney Injury		
None	59 (83.0)	52 (76.4)
Stage 1	7 (9.8)	7 (10.2)
Stage 2	2 (2.8)	7 (10.2)
Stage 3	3 (4.2)	2 (2.9)
Total MV duration (min.)	736 [420 – 1492]	780 [436 – 1510]
ICU stay (h)	27 [20 - 70]	27 [22 - 47]
Hospital stay (days)	9 [7 – 12]	8 [7 - 11]
Arrhythmias	11	7
Reoperation for bleeding control	1 (1.4)	0
Re-intubation	2 (2.8)	0

Data are present as mean (SD) or median [IQR], or n (%). Arrhythmias; atrial premature complex, ventricular premature complex, junctional ectopic tachycardia, MV; mechanical ventilation, ICU; intensive care unit

Table 3 Subgroup analysis according to the diagnosis and CPB duration

	Patients with VSD		**Patients other than VSD**	
	Dexmedetomidine group (n=31)	Control group (n=32)	Dexmedetomidine group (n=40)	Control group (n=36)
No AKI	28 (90.3)	23 (71.8)	31 (77.5)	29 (80.6)
AKI	3 (9.7)	9 (28.1)	9 (22.5)	7 (19.4)
P value	0.062		0.742	
	CPB time >= 180min.		**CPB time < 180min.**	
	Dexmedetomidine group (n=18)	Control group (n=17)	Dexmedetomidine group (n=53)	Control group (n=51)
No AKI	12 (66.6)	11 (64.7)	47 (88.6)	41 (80.3)
AKI	6 (33.3)	6 (35.2)	6 (11.3)	10 (19.6)
P value	0.902		0.241	

Data are present as n (%). AKI; acute kidney injury, VSD; ventricular septal defect, CPB; cardiopulmonary bypass

Table 4 Perioperative laboratory data in the dexmedetomidine and control group

	Dexmedetomidine group (n=71)	Control Group (n=68)
Preoperative laboratory data		
WBC (10^3 /μl)	9.4 (3.2)	9.6 (2.6)
Hg (g/dl)	12.9 (2.5)	12.7 (2.4)
Hematocrit (%)	39.2 (7.6)	37.7 (7.0)
Platelet (10^3/μl)	322.4 (96.4)	350.5 (93.1)
INR	1.07 (0.11)	1.05 (0.07)
aPTT (sec)	38.3 (3.8)	36.0 (4.3)
Fibrinogen (mg/dl)	233.0 (67.9)	242.4 (58.6)
Albumin (g/dl)	4.3 (0.3)	4.2 (0.3)
AST (IU/L)	35.0 [29.5 – 41.0]	34.0 [29.0 – 41.0]
ALT (IU/L)	21.0 [13.0 – 27.5]	19.0 [15.0 -- 24.0]
Creatinine (mg/dl)	0.31	0.31
eGFR (ml/min/1.73 m^2)	107.0 (22.3)	107.2 (26.9)
Na (mmol/L)	138.0 (1.6)	138.3 (1.7)
K (mmol/L)	4.5 (0.7)	4.7 (0.6)
Cl (mmol/L)	106.2 (2.3)	104.7 (12.9)
Hs-CRP (mg/dl)	0.05 [0.03-0.12]	0.04 [0.02-0.06]
Glucose (mg/dl)	98.5 (21.9)	97.8 (13.9)
Intraoperative fluid variables		
Crystalloids (ml/kg/h)	20.7 (6.9)	19.2 (7.1)
Red blood cells	110 [75 – 150]	130 [100 - 175]
Red blood cells (ml/kg)	12.3 [7.5-18.7]	11.9 [8.6-21.9]
Fresh frozen plasma	0 [0 – 0]	0 [0 – 0]
Platelet pheresis	0 [0 – 0]	0 [0 – 0]
Albumin	22.8 (7.0)	23.9 (6.7)
Urine output (ml/kg/h)	10.8 (5.3)*	5.8 (5.1)
Cardiopulmonary bypass urine output (ml/kg/h)	19.9 (11.2)*	11.5 (12.2)
Postoperative laboratory data		
Immediate postoperative creatinine (mg/dl)	0.30 (0.07)*	0.33 (0.08)

Immediate postoperative eGFR (ml/min/1.73 m^2)	108.4 (30.1)*	97.7 (24.9)
Immediate postoperative urine output (ml/kg/h)	3.3 (1.8)	3.8 (4.5)
Immediate post op weight gain (kg)	-0.01 (0.51)	-0.04 (0.54)

Data are present as mean (SD) or median [IQR], or n (%). * $p < 0.05$

Table 5 Postcardiopulmonary bypass rotational thromboelastometry variables in dexmedetomidne and control group.

	Dexmedetomidine group (n=71)	Control group (n=68)	P- value
EXTEM_clotting time	110.5 (22.4)	102.0 (19.3)	0.018
EXTEM_clot firmness time	205.1 (90.0)	175.5 (58.7)	0.024
EXTEM_alpha angle	56.1 (8.4)	58.8 (7.3)	0.045
EXTEM_amplitude at 10min.	37.7 (7.0)	40.5 (6.8)	0.019
EXTEM_amplitude at 20 min.	45.2 (6.8)	48.1 (6.7)	0.011
EXTEM_maximal clot firmness	47.3 (7.9)	50.8 (6.5)	0.005
EXTEM_maximal lysis	4.5 (10.7)	2.7 (3.6)	0.177
FIBTEM_clotting time	174.6 (277.8)	117.6 (61.6)	0.101
FIBTEM_amplitude at 10min.	5.7 (2.2)	7.5 (9.3)	0.117
FIBTEM_amplitude at 20min.	6.3 (2.4)	6.6 (2.1)	0.506
FIBTEM_maximal clot firmness	6.6 (2.7)	6.7 (2.6)	0.702
FIBTEM_maximal lysis	10.3 (19.4)	7.4 (11.5)	0.290

Data are present as mean (SD) or median [IQR]

Table 6 Parameter estimates (RSE, % CV) of competing basic and covariate pharmacokinetic models of dexmedetomidine

	Model 1	Model 2*	Model 3	Model 4†
Covariate	-	-	V_1: CPB	V_1: CPB, WT
V_1, (L)	5.14 (13.9, 55.7)	5.07 (8.2, 29.9)	CPB_off: 5.45 (10.7, 42.3)	CPB_off: $5.92\times(WT/10)^{0.641}$ (8.4, 28.5)
			CPB_on: 19.1 (14.7, 42.3)	CPB_on: $19.4\times(WT/10)^{0.641}$ (14.7, 28.5)
V_2, (L)	–	120 (44.9, 85.2)	147 (24.4, 127.3)	$146\times(WT/10)^{0.641}$ (25.5, 126.1)
Cl, (L/min)	0.354 (8.1, 42.4)	0.133 (46.8, 69.3)	0.0801 (13.2, –)	$0.101\times(WT/10)^{0.52}$ (13.6, –)
Q, (l/min)	–	0.36 (16.4, 35.5)	0.382 (9.2, 45.2)	$0.397\times(WT/10)^{0.52}$ (7.4, 37.4)
OFV	–586.96	–752.38	–796.21	–821.60
Number of parameters (p)	5	9	9	9

AIC	−576.96	−734.38	−778.21	−799.60

OFV: objective function value (−2 log likelihood, −2LL); AIC: Akaike information criteria (−2LL + 2× p); CV: coefficient of variation; RSE: relative standard error = SE/estimate × 100 (%); CPB: cardiopulmonary bypass, CPB_off: not applied, CPB_on: applied, V_1: central volume of distribution; V_2: rapid peripheral volume of distribution; *Cl*: metabolic clearance; *Q*: inter-compartmental clearance of rapid peripheral compartment. ; σ^2, variance of residual random variability.

Table 7 Population pharmacokinetic parameter estimates and results of non-parametric bootstrap replicates of the final pharmacokinetic model of dexmedetomidine

Parameters**		Estimates (RSE, %)	CV (%)	Median (2.5–97.5%)
V_1 (L) = θ_1 × (WT/10)$^{\theta_2}$	θ_1	5.92 (8.4)	28.5	5.95 (5.32–6.58)
	θ_2	0.641 (23.7)	–	0.66 (0.44–0.90)
V_{1_CPB} (L) = θ_3 × (WT/10)$^{\theta_2}$	θ_3	19.4 (14.7)	28.5	18.8 (14.7–22.9)
V_2 (L) = θ_4 × (WT/10)$^{\theta_2}$	θ_4	146 (25.5)	126.1	148 (106–295)
Cl (L/min) = θ_4 × (WT/10)$^{\theta_5}$	θ_4	0.101 (13.6)	–	0.102 (0.0008–0.131)
	θ_5	0.52 (24.4)	–	0.54 (0.32–0.73)
Q (L/min) = θ_6 × (WT/10)$^{\theta_5}$	θ_6	0.397 (7.4)	37.4	0.387 (0.345–0.461)
σ^2 (%)		0.13 (14.9)		0.13 (0.006–0.14)

*selected basic model. †selected final model. **A log-normal distribution of inter-individual random variability was assumed. Residual random variability was modeled using a constant coefficient of variation model. Non-parametric bootstrap analysis was repeated 2,000 times

Figures

Figure 1 CONSORT flow diagram

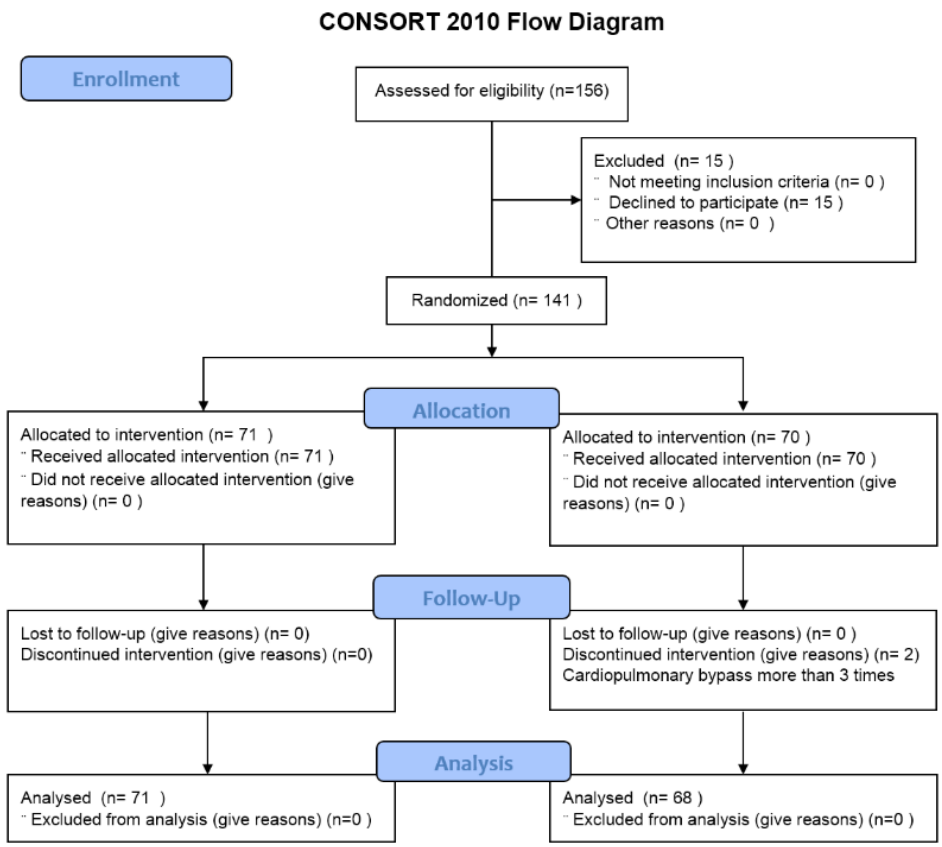


Figure 2 Perioperative changes of creatinine, eGFR, lactate, and urine output in dexmedetomidine and control group

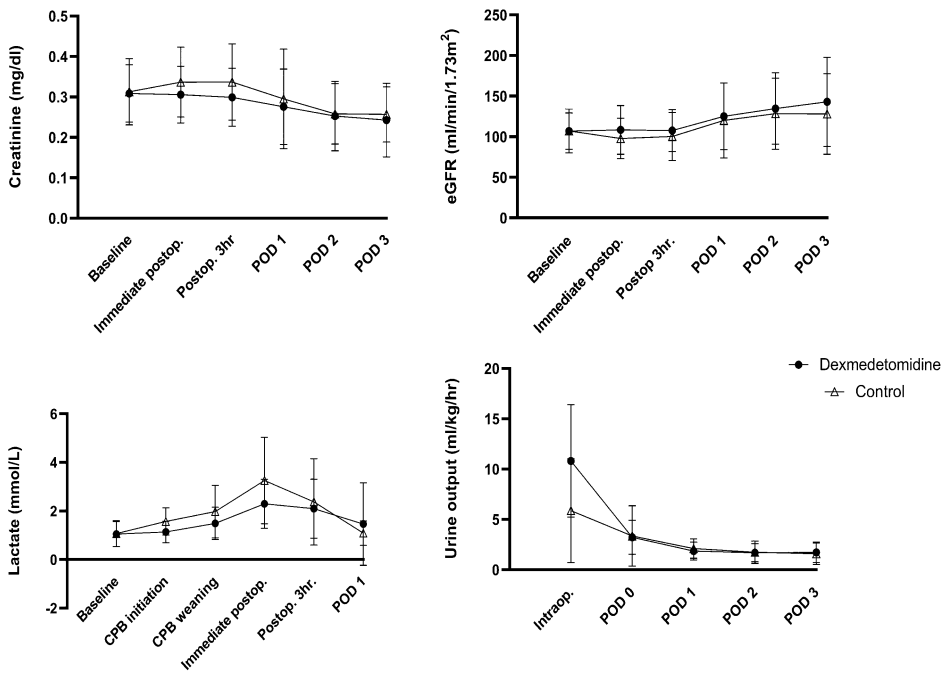


Figure 3 Changes of heart rate and mean blood pressure with dexmedetomidine infusion

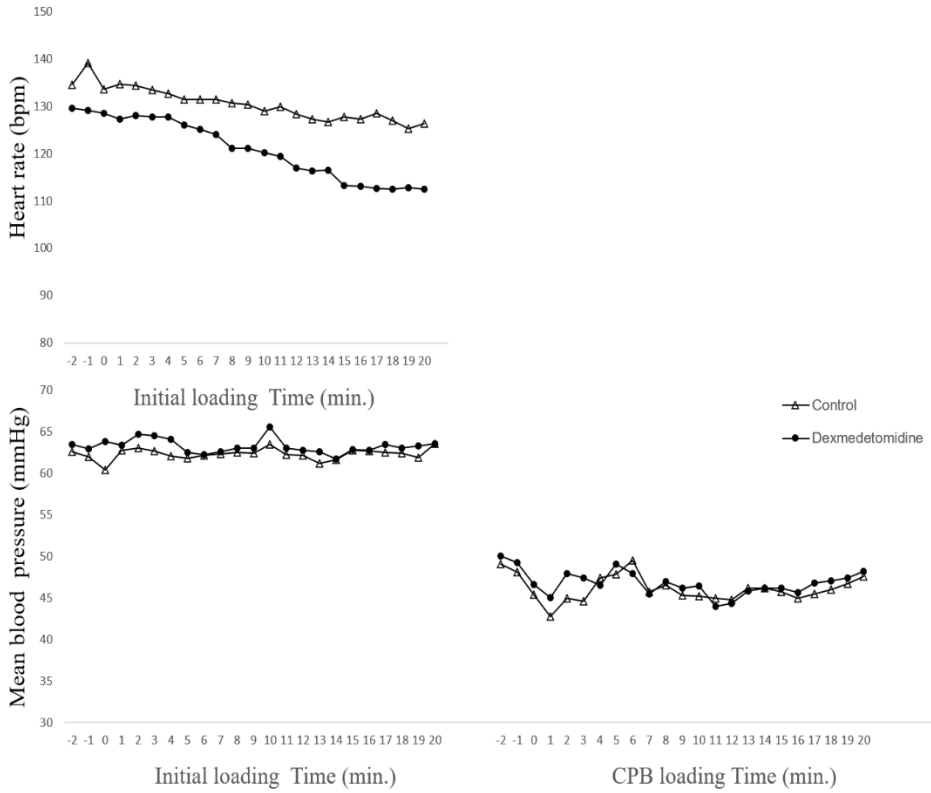


Figure 4 Dexmedetomidine concentration individual plot 1

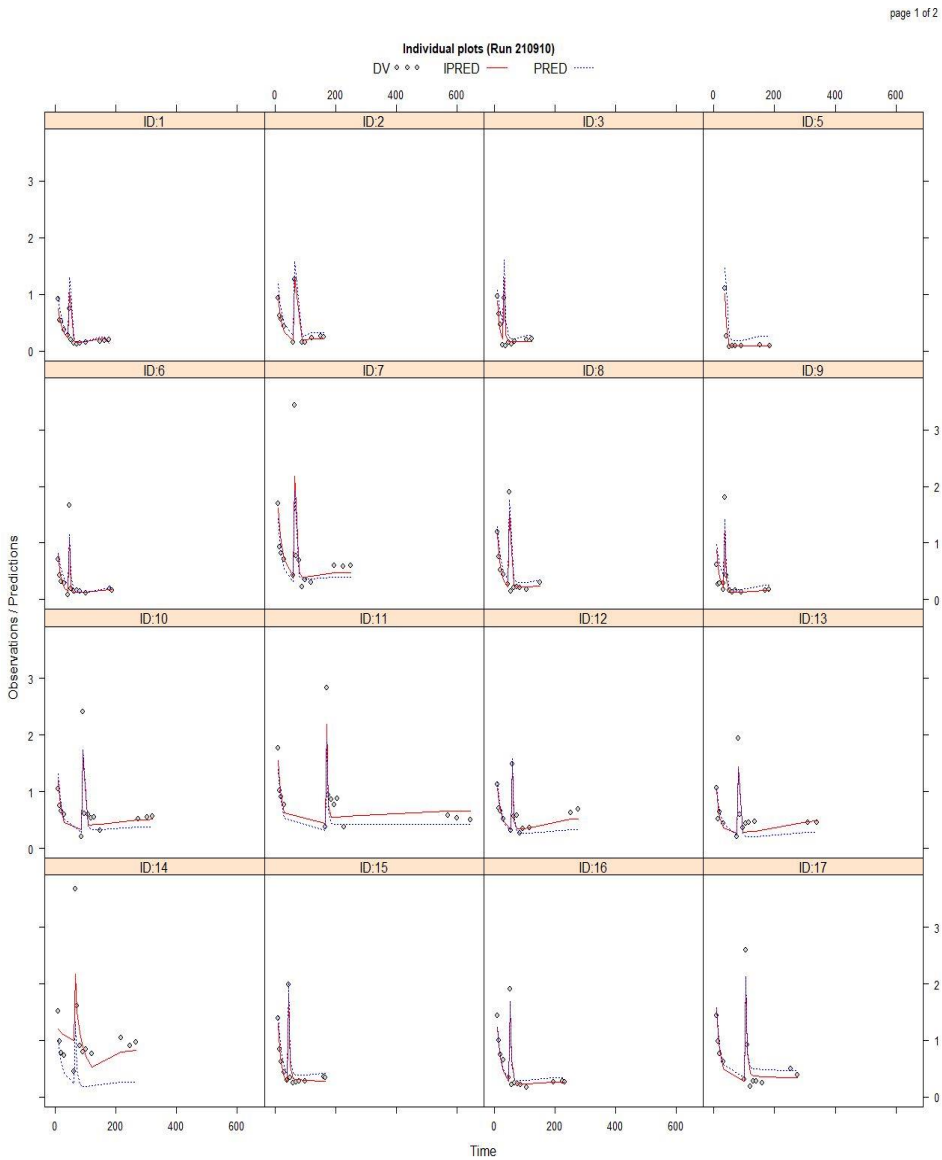


Figure 5 Dexmedetomidine concentration individual plot 2

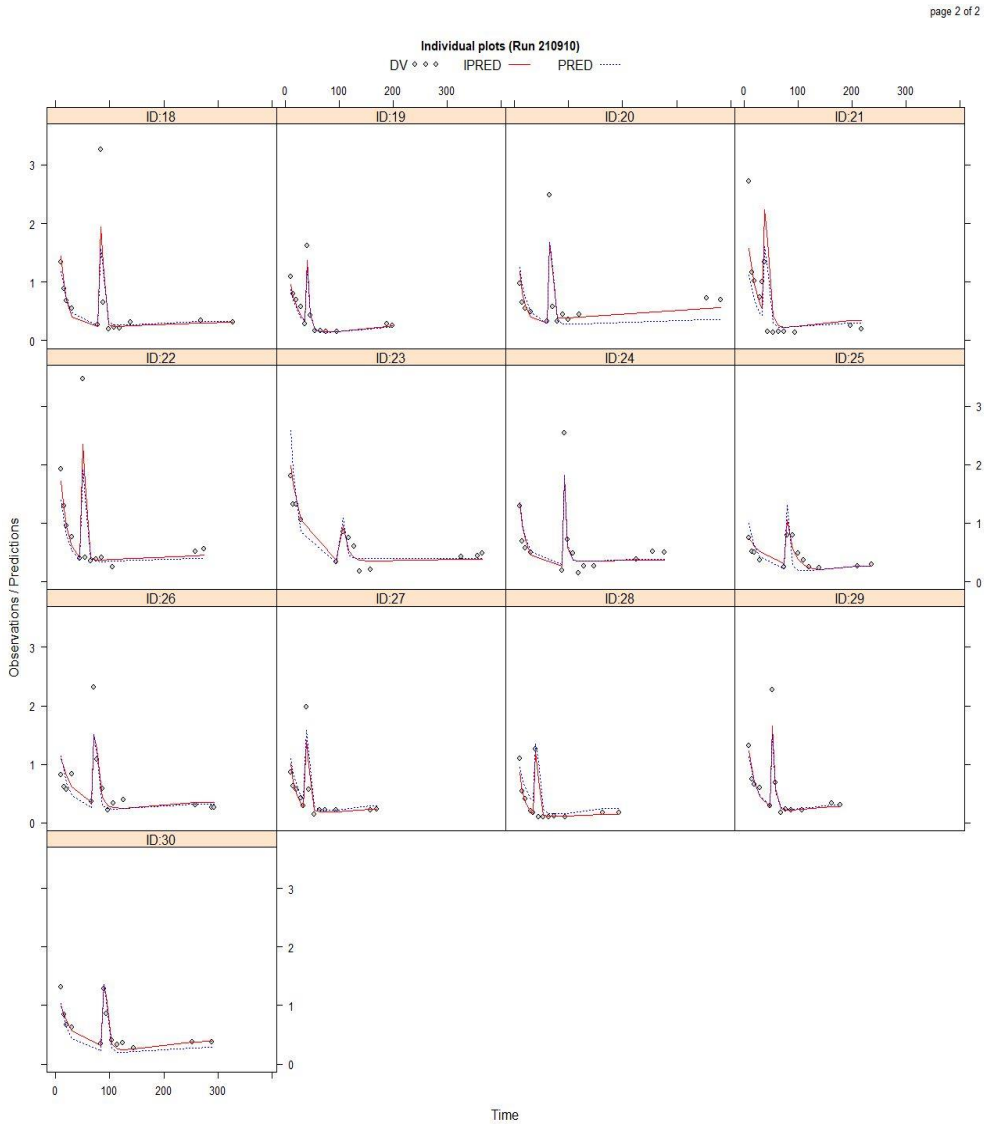
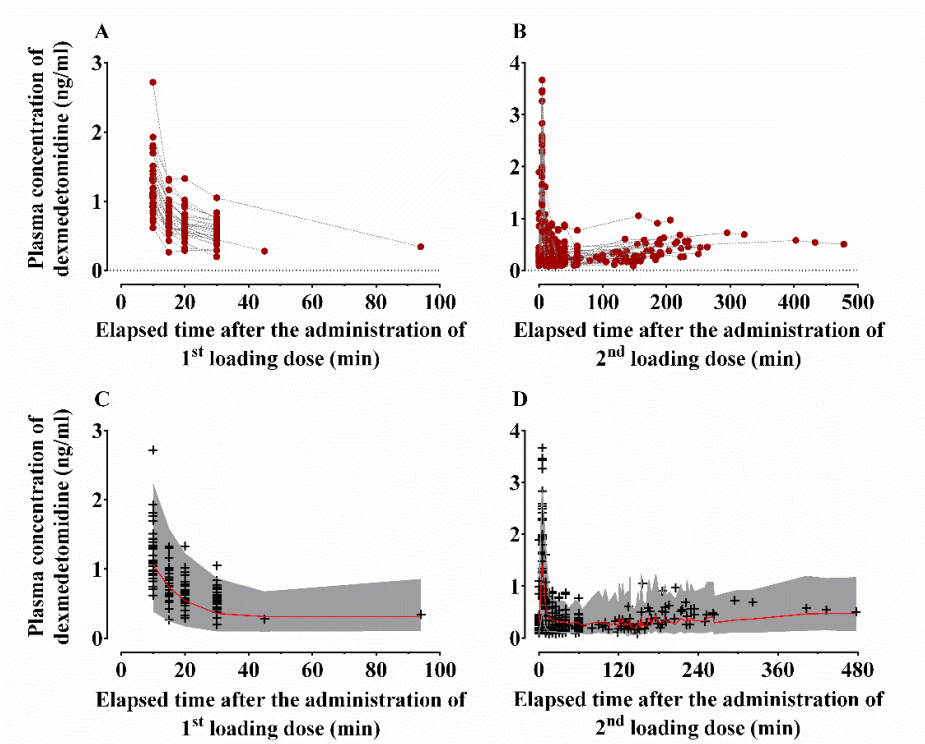
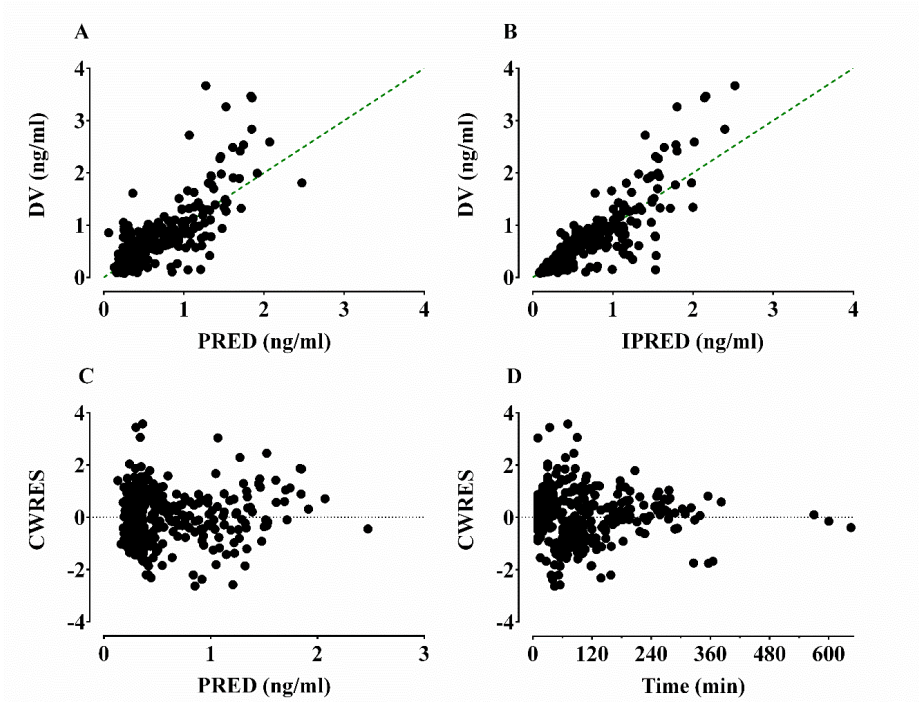


Figure 6 Measured plasma concentrations of dexmedetomidine (A, B) over time in 29 children and predictive checks (C,D) of the final pharmacokinetic model for dexmedetomidine.



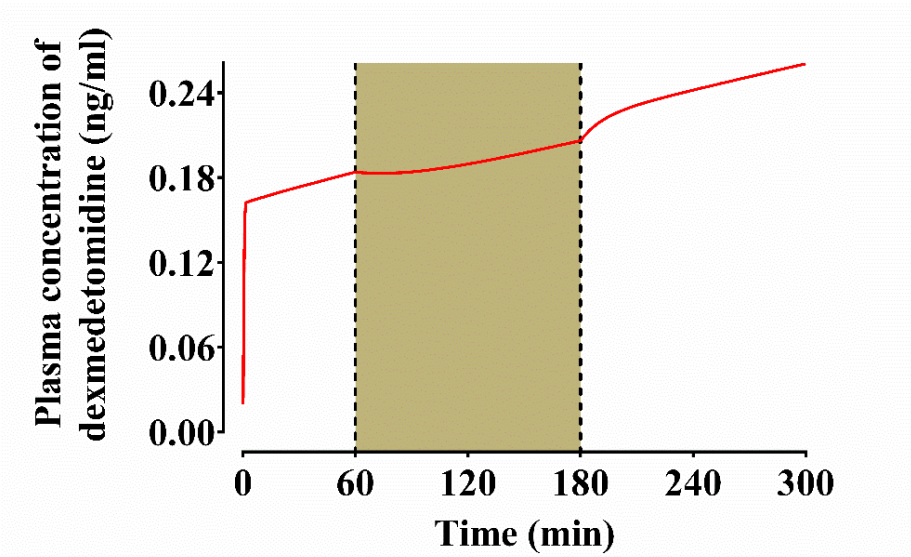
Children received a loading dexmedetomidine infusion of 1 μg/kg for 10 min followed by continuous infusion at a rate of 0.5 μg/kg/huntil the end of surgery. In addition, a second loading dose of 1 μg/kg was administered for 5 minutes before implementing cardiopulmonary bypass (CPB). The red solid line and shaded areas indicate the 50% prediction line and 90% prediction intervals, respectively. +: measured plasma concentration of dexmedetomidine.

Figure 7 Goodness-of- fit plots of the final pharmacokinetic model for dexmedetomidine.



A: PRED (population predicted plasma concentration of dexmedetomidine) vs. DV (measured plasma concentration of dexmedetomidine), B: IPRED (individually predicted plasma concentration of dexmedetomidine) vs. DV, C: conditional weighted residuals (CWRES) vs. PRED, D: CWRES over time. The dashed line is the line of identity.

Figure 8 Simulated time course of plasma concentration of dexmedetomidine in a hypothetical child weighing 10 kg



After administration of a loading dexmedetomidine infusion of 1 μg/kg for 10 min followed by continuous infusion at a rate of 0.5 μg/kg/h during 290 min in a hypothetical child weighing 10 kg. The brown shaded area represents the cardiopulmonary bypass (CPB) period (120 min).

4 Discussion

4.1 Incidence of AKI

This study demonstrates that intraoperative dexmedetomidine does not reduce the overall incidence of AKI in pediatric patients who underwent congenital cardiac surgery.

Dexmedetomidine is a selective α_2- adrenoreceptor agonist which can provide analgesia and anxiolysis with minimal respiratory depression (28). Through the α_2- adrenoreceptor, dexmedetomidine has sympatholytic effects, resulting in hemodynamic stability and mitigating renal ischemic- reperfusion injury (29-31). Also, dexmedetomidine improves tubular architecture and function following renal ischemia (32).

A growing body of literature in animal studies suggest the effects of dexmedetomidine on major organ protection are due to diminishing ischemia and hypoxic injury and reduced systemic inflammatory response in various conditions (33). Previous studies have reported that dexmedetomidine has a renoprotective effect in adult patients undergoing cardiac surgery under CPB (7, 8, 34). However, studies that have focused on the effects of dexmedetomidine in pediatric patients are limited. Jo et al. conducted a small randomized controlled trial that investigated the effects of intraoperative dexmedetomidine

on the incidence of AKI, which was defined as an increase in serum creatinine in 29 patients (12). However, the sample size was too small and only included atrial or ventricular septal defect repair patients who had a low risk of renal complication (3, 35) ; therefore, it was difficult to generalize these findings to other samples.

Here, we conducted a randomized controlled trial that included a relatively large number of pediatric cardiac patients to evaluate the effects of dexmedetomidine on AKI using the KIDIGO guideline. We found that the incidence of AKI was not different between the two groups. Although, we used stratified randomization assignment based on RACHS criteria, the types of procedures were variable from simple VSD repair to complex cardiac surgery, accordingly, the duration of CPB also showed wide range. We performed subgroup analysis to minimize confounding effects of types of surgery and CPB duration. The incidence of AKI seemed much more reduced in the dexmedetomidine group (9.7%) compared with control group (28.1%) only in patients with VSD. It would have been difficult to differentiate the renoprotective effect of dexmedetomidine in patients undergoing complex cardiac surgery because of the large number of factors affecting the occurrence of AKI in these patients. However, in patients undergoing simple VSD repair, the renoprotective effects of dexmedetomidine could be identified beyond other factors related with the renal injury. Therefore, perioperative dexmedetomidine could have possible

renoprotective effect in pediatric patients undergoing cardiac surgery.

Serum creatinine values are influenced by multiple non-renal factors (36). Additionally, there is a delayed increase in serum creatinine values after AKI. The use of more sensitive biomarkers, such as serum cystatin C or neutrophil gelatinase-associated lipocalin (NGAL), may have allowed for a more accurate assessment of renal function during the early postoperative period (37).

However, serum creatinine remains the standard for diagnosing AKI and is a reliable predictor of AKI after cardiac surgery (38). Also, numerous studies reported that small changes in serum creatinine levels are associated with significant changes in outcomes (39-41). For example, Tolpin et al. (41) demonstrated that a 0.1–0.2 mg/dL increase in creatine levels (and <50% increase from baseline) was associated with a 3.9-fold increase in 30-day all-cause mortality in adults after cardiac surgery. In this study, the immediate postoperative creatinine was increased by 3% from the baseline in the dexmedetomidine group, whereas creatinine was increased by 12% in the control group. Recent studies have suggested that hyperlactatemia may be linked to the development of AKI after cardiac surgery (42). Although these changes may be small and clinically insignificant, they may demonstrate the renoprotective effects of dexmedetomidine.

The immediate post-CPB EXTEM clotting and clot firmness times were

significantly longer and the EXTEM alpha angle, A10, A20, and MCF were significantly shorter in the dexmedetomidine group than those in the control group. There were no significant differences in the FIBTEM variables between the two groups. Additionally, the preoperative and postoperative coagulation profile, transfusion amount, and the incidence of re-exploration for bleeding control were not significantly different between the two groups. Chen et al. investigated the effect of dexmedetomidine on blood coagulation in patients with radical gastrectomy and found that adjunctive dexmedetomidine with general anesthesia attenuated postoperative hypercoagulation (43). They postulated that the anti-inflammatory effects of dexmedetomidine (44, 45) reduced the perioperative stress response, and resulted in prevention of coagulation following surgery (46, 47).

In the current study, dexmedetomidine was only administered intraoperatively; however, Kwiatkowski et al. conducted a cohort study that included 102 patients who received dexmedetomidine after cardiac surgery. These researchers reported that the continuous infusion of postoperative dexmedetomidine reduced the incidence of AKI after congenital heart surgery (13). Furthermore, Cho et al. reported that the incidence of AKI was reduced in adult patients when dexmedetomidine was infused at a rate of 0.4 μg/kg/h at the beginning of anesthetic induction until 24 h after valvular heart surgery (8). Therefore, additional postoperative infusions may enhance the effects of dexmedetomidine

after cardiac surgery.

Transfusion of red blood cells is an important risk factor for developing perioperative AKI (48, 49). We compared patients with or without a large amount of red blood cell transfusion. The incidence of AKI was higher in patients with large blood volume transfusion regardless of using dexmedetomidine or not.

Some previous randomized controlled trials demonstrated that dexmedetomidine significantly reduced the incidence of perioperative arrhythmias (50), major morbidity end points, and the length of stay in the intensive care unit (8). However, we did not observe any differences in the incidence of perioperative arrhythmia, length of mechanical ventilation, length of stay in the intensive care unit, and hospitalization between the two groups. In the current study, the mean mechanical ventilation duration was 23 hours and the mean length of stay in the intensive care unit was 60 hours. Given the short duration of mechanical ventilation and stay in the intensive care unit, renal protection was unlikely associated with the changes in clinical outcomes in the current study. The association of renal protection with clinical outcomes may have been more robust if this analysis included higher risk patients, such as neonates.

4.2 Population pharmacokinetic analysis

Population pharmacokinetic analysis showed that the CPB was a significant covariate for the central volume of distribution, with marked increment with presence of CPB. Meanwhile, clearance was not influenced by presence of CPB. Contrary to our results, several previous reports also showed marked diminished dexmedetomidine clearance during and after CPB due to decreased hepatic flow from lowered cardiac output and hypothermia during CPB (51-53). We did not measure cardiac output before and after the CPB, but we could conjecture that it was maintained in our patients. Also, we used normothermic bypass not hypothermic, it could contribute maintained clearance of dexmedetomidine in our patients. Further studies considering the effects of real-time cardiac output monitoring and temperature management for providing proper dosing regimen is needed. However, in this study, the change in plasma concentration during CPB was not prominent in simulation. We can suggest that the use of dexmedetomidine in pediatric patients undergoing cardiac surgery without adjustment of dosage or addition of a loading dose at the beginning of CPB. There needs further study to validate optimal therapeutic concentration of dexmedetomidine to prevent AKI in pediatric patients undergoing cardiac surgery.

4.3 Limitations

This study had several limitations. First, we only included patients in RACHS categories 2 and 3 with normal renal function and excluded neonates who are at the highest risk for AKI and associated adverse outcomes because we wanted to avoid potential biases (35, 54). However, our results cannot be extrapolated beyond this sample of patients. Therefore, the generalizability of these results may be reduced. Second, the mechanism of renal injury during cardiac surgery with CPB was multifactorial. Even though we only enrolled patients in RACHS categories 2 and 3, included patients had a wide range of surgical complexities and physiologic differences (single or biventricular physiology), which could affect perioperative renal function. Third, we calculated the sample size based on the incidence of AKI from our previous study (40.8%). However, the overall incidence of AKI was smaller in this study than that in our previous study. Furthermore, for subgroup analysis, the sample size was too small to draw a conclusion. A larger sample size will increase the differences in the incidence of AKI and clinical outcomes.

5 Conclusion

In conclusion, intraoperative of dexmedetomidine did not reduce the overall incidence of AKI in pediatric patients with preoperative normal renal function, receiving RACHS category 2 and 3 cardiac surgery.

6 References

1. Hirano D, Ito A, Yamada A, Kakegawa D, Miwa S, Umeda C, et al. Independent Risk Factors and 2-Year Outcomes of Acute Kidney Injury after Surgery for Congenital Heart Disease. American journal of nephrology. 2017;46(3):204-9.

2. Madsen NL, Goldstein SL, Froslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int. 2017;92(3):751-6.

3. Lee JH, Jung JY, Park SW, Song IK, Kim EH, Kim HS, et al. Risk factors of acute kidney injury in children after cardiac surgery. Acta anaesthesiologica Scandinavica. 2018;62(10):1374-82.

4. Leow EH, Chan YH, Ng YH, Lim JKB, Nakao M, Lee JH. Prevention of Acute Kidney Injury in Children Undergoing Cardiac Surgery: A Narrative Review. World journal for pediatric & congenital heart surgery. 2018;9(1):79-90.

5. Schetz M, Bove T, Morelli A, Mankad S, Ronco C, Kellum JA. Prevention of cardiac surgery-associated acute kidney injury. The International journal of artificial organs. 2008;31(2):179-89.

6. Gude D, Jha R. Acute kidney injury following cardiac surgery. Ann Card Anaesth. 2012;15(4):279-86.

7. Kim WH, Hur M, Park SK, Jung DE, Kang P, Yoo S, et al. Pharmacological interventions for protecting renal function after cardiac surgery: a Bayesian network

meta-analysis of comparative effectiveness. Anaesthesia. 2018;73(8):1019-31.

8. Cho JS, Shim JK, Soh S, Kim MK, Kwak YL. Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery. Kidney Int. 2016;89(3):693-700.

9. Van Driest SL, Jooste EH, Shi Y, Choi L, Darghosian L, Hill KD, et al. Association Between Early Postoperative Acetaminophen Exposure and Acute Kidney Injury in Pediatric Patients Undergoing Cardiac Surgery. JAMA pediatrics. 2018;172(7):655-63.

10. Bellos I, Iliopoulos DC, Perrea DN. Pharmacological interventions for the prevention of acute kidney injury after pediatric cardiac surgery: a network meta-analysis. Clin Exp Nephrol. 2019;23(6):782-91.

11. Simpson SA, Zaccagni H, Bichell DP, Christian KG, Mettler BA, Donahue BS, et al. Acetaminophen attenuates lipid peroxidation in children undergoing cardiopulmonary bypass. Pediatr Crit Care Med. 2014;15(6):503-10.

12. Jo YY, Kim JY, Lee JY, Choi CH, Chang YJ, Kwak HJ. The effect of intraoperative dexmedetomidine on acute kidney injury after pediatric congenital heart surgery: A prospective randomized trial. Medicine (Baltimore). 2017;96(28):e7480.

13. Kwiatkowski DM, Axelrod DM, Sutherland SM, Tesoro TM, Krawczeski CD. Dexmedetomidine Is Associated With Lower Incidence of Acute Kidney Injury After Congenital Heart Surgery. Pediatr Crit Care Med. 2016;17(2):128-34.

14. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. The Journal of thoracic and cardiovascular surgery. 2002;123(1):110-8.

15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84.

16. Luo X, Jiang L, Du B, Wen Y, Wang M, Xi X. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. Crit Care. 2014;18(4):R144.

17. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015;87(1):62-73.

18. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.

19. Germovsek E, Barker CI, Sharland M, Standing JF. Scaling clearance in paediatric pharmacokinetics: All models are wrong, which are useful? Br J Clin Pharmacol. 2017;83(4):777-90.

20. Holford NH, Anderson BJ. Why standards are useful for predicting doses. Br J Clin Pharmacol. 2017;83(4):685-7.

21. Heilbron DC, Holliday MA, al-Dahwi A, Kogan BA. Expressing glomerular filtration rate in children. Pediatr Nephrol. 1991;5(1):5-11.

22. Yoo YC, Shim JK, Song Y, Yang SY, Kwak YL. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. Kidney Int. 2014;86(2):414-22.

23. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clinical pharmacokinetics. 2005;44(10):1051-65.

24. Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofsen E, Vuyk J, et al. An Allometric Model of Remifentanil Pharmacokinetics and Pharmacodynamics. Anesthesiology. 2017;126(6):1005-18.

25. Park JH, Choi SM, Park JH, Lee KH, Yun HJ, Lee EK, et al. Population pharmacokinetic analysis of propofol in underweight patients under general anaesthesia. Br J Anaesth. 2018;121(3):559-66.

26. Choi BM, Lee YH, An SM, Lee SH, Lee EK, Noh GJ. Population pharmacokinetics and analgesic potency of oxycodone. Br J Clin Pharmacol. 2017;83(2):314-25.

27. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten SE. Effects of Cardiopulmonary Bypass on Renal Perfusion, Filtration, and Oxygenation in Patients Undergoing Cardiac Surgery. Anesthesiology. 2017;126(2):205-13.

28. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. British journal of anaesthesia. 2015;115(2):171-82.

29. Gellai M, Ruffolo RR, Jr. Renal effects of selective alpha-1 and alpha-2 adrenoceptor agonists in conscious, normotensive rats. J Pharmacol Exp Ther. 1987;240(3):723-8.

30. Myles PS, Hunt JO, Holdgaard HO, McRae R, Buckland MR, Moloney J, et al. Clonidine and cardiac surgery: haemodynamic and metabolic effects, myocardial ischaemia and recovery. Anaesth Intensive Care. 1999;27(2):137-47.

31. Villela NR, do Nascimento Júnior P, de Carvalho LR, Teixeira A. Effects of dexmedetomidine on renal system and on vasopressin plasma levels. Experimental study in dogs. Rev Bras Anestesiol. 2005;55(4):429-40.

32. Gu J, Sun P, Zhao H, Watts HR, Sanders RD, Terrando N, et al. Dexmedetomidine provides renoprotection against ischemia-reperfusion injury in mice. Crit Care. 2011;15(3):R153.

33. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Critical care medicine. 2004;32(6):1322-6.

34. Honore PM, De Bels D, Preseau T, Spapen HD. Dexmedetomidine: the first new kid on the block for preventing cardiac surgery-associated acute kidney injury? Crit Care. 2018;22(1):151.

35. Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Critical care medicine.

2011;39(6):1493-9.

36. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clinical journal of the American Society of Nephrology : CJASN. 2008;3(2):348-54.

37. Krawczeski CD, Vandevoorde RG, Kathman T, Bennett MR, Woo JG, Wang Y, et al. Serum cystatin C is an early predictive biomarker of acute kidney injury after pediatric cardiopulmonary bypass. Clinical journal of the American Society of Nephrology : CJASN. 2010;5(9):1552-7.

38. Grynberg K, Polkinghorne KR, Ford S, Stenning F, Lew TE, Barrett JA, et al. Early serum creatinine accurately predicts acute kidney injury post cardiac surgery. BMC nephrology. 2017;18(1):93.

39. Praught ML, Shlipak MG. Are small changes in serum creatinine an important risk factor? Current opinion in nephrology and hypertension. 2005;14(3):265-70.

40. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Critical care medicine. 2008;36(4):1129-37.

41. Tolpin DA, Collard CD, Lee VV, Virani SS, Allison PM, Elayda MA, et al. Subclinical changes in serum creatinine and mortality after coronary artery bypass

grafting. The Journal of thoracic and cardiovascular surgery. 2012;143(3):682-8.e1.

42. Radovic M, Bojic S, Kotur-Stevuljevic J, Lezaic V, Milicic B, Velinovic M, et al. Serum Lactate As Reliable Biomarker of Acute Kidney Injury in Low-risk Cardiac Surgery Patients. Journal of medical biochemistry. 2019;38(2):118-25.

43. Chen Z, Shao DH, Mao ZM, Shi LL, Ma XD, Zhang DP. Effect of dexmedetomidine on blood coagulation in patients undergoing radical gastrectomy under general anesthesia: A prospective, randomized controlled clinical trial. Medicine (Baltimore). 2018;97(27):e11444.

44. Wang XW, Cao JB, Lv BS, Mi WD, Wang ZQ, Zhang C, et al. Effect of perioperative dexmedetomidine on the endocrine modulators of stress response: a meta-analysis. Clinical and experimental pharmacology & physiology. 2015;42(8):828-36.

45. Dong W, Chen MH, Yang YH, Zhang X, Huang MJ, Yang XJ, et al. The effect of dexmedetomidine on expressions of inflammatory factors in patients with radical resection of gastric cancer. European review for medical and pharmacological sciences. 2017;21(15):3510-5.

46. Rosenfeld BA, Faraday N, Campbell D, Dise K, Bell W, Goldschmidt P. Hemostatic effects of stress hormone infusion. Anesthesiology. 1994;81(5):1116-26.

47. Liuboshevskii PA, Artamonova NI, Ovechkin AM. [Haemostasis disturbances as the component of the surgical stress-response and possibilities of their correction]. Anesteziologiia i reanimatologiia. 2012(3):44-8.

48. Karkouti K. Transfusion and risk of acute kidney injury in cardiac surgery. British journal of anaesthesia. 2012;109 Suppl 1:i29-i38.

49. Park SK, Hur M, Kim E, Kim WH, Park JB, Kim Y, et al. Risk Factors for Acute Kidney Injury after Congenital Cardiac Surgery in Infants and Children: A Retrospective Observational Study. PloS one. 2016;11(11):e0166328.

50. El Amrousy DM, Elshmaa NS, El-Kashlan M, Hassan S, Elsanosy M, Hablas N, et al. Efficacy of Prophylactic Dexmedetomidine in Preventing Postoperative Junctional Ectopic Tachycardia After Pediatric Cardiac Surgery. J Am Heart Assoc. 2017;6(3).

51. Su F, Gastonguay MR, Nicolson SC, DiLiberto M, Ocampo-Pelland A, Zuppa AF. Dexmedetomidine Pharmacology in Neonates and Infants After Open Heart Surgery. Anesth Analg. 2016;122(5):1556-66.

52. Zimmerman KO, Wu H, Laughon M, Greenberg RG, Walczak R, Schulman SR, et al. Dexmedetomidine Pharmacokinetics and a New Dosing Paradigm in Infants Supported With Cardiopulmonary Bypass. Anesth Analg. 2018.

53. Zuppa AF, Nicolson SC, Wilder NS, Ibla JC, Gottlieb EA, Burns KM, et al. Results of a phase 1 multicentre investigation of dexmedetomidine bolus and infusion in corrective infant cardiac surgery. British journal of anaesthesia. 2019;123(6):839-52.

54. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. The

Journal of thoracic and cardiovascular surgery. 2012;143(2):368-74.

7 국문요약

요약 (국문초록)

심장 수술을 받는 소아에서 덱스메데토미딘의 신보호 효과 : 무작위 배정 연구

연구배경 및 중요성: 주술기 급성 신손상은 수술 후 이환율과 사망률을 증가시키며, 소아에서 그 발생 빈도는 35-50% 로 보고된다. 이를 감소시키기 위한 다양한 방법이 제시되고 있고, 최근 성인의 연구에서 주술기 덱스메데토미딘의 주입이 급성 신손상의 빈도를 줄였다. 소아에서는 그 연구가 아직 부족하여 주술기 사용에 대한 근거가 부족하다. 이에 본 연구에서는 덱스메데토미딘의 사용이 주술기 급성 신손상을 감소시킬 수 있는지 알아보고, 적정 용량을 주입하기 위해 약동학을 함께 확인해보고자 한다.

연구방법: 이중 눈가림 무작위 배정 연구로 선천성 심장질환으로 수술을 받는 7세 미만의 환아 141명을 대상으로 연구를 진행하였다. 마취 유도 후 덱스메데토미딘군은 덱스메데토미딘 1 μg/kg을 10분에 걸쳐 주입하고, 이후 0.5 μg/kg/h로 지속 주입하였다. 이후 심폐우회술 시작 시 1 μg/kg을 추가적으로 주입하였으며, 대조군은 동량의 생리식염수를 주입하였다. 덱스메데토미딘군 중 30명을 대상으로 약동학 분석을 위한 샘플을 시행하였고, 약동학은 NONMEM VII을 이용하여 분석하였다.

평가변수: 일차 평가변수는 Kidney Disease Improving Global Outcomes guidelines에 따른 두 군의 급성 신손상의 발생 빈도의 차이이며 주요 이차 평가변수는 덱스메데토미딘의 약동학에 심폐우회술이 미치는 영향을 확인하는 것이다.

연구결과: 최종 139명을 분석하였고, 급성신손상의 발생은 두 군에서 다르지 않았다 (16.9% vs. 23.5%; odds ratio 0.661; 95% CI 0.285 to 1.525; p = 0.339). 하지만 수술 중 소변량은 덱스메데토미딘군에서 많았고 (mean difference [95% CI]; 4.9 ml/kg/h [3.1 to 6.7 ml/kg/h], p = 0.001), 수술 후 측정한 크레아티닌은 덱스메데토미딘군에서 낮았다 (mean difference [95% CI]; -0.03 mg/dl [-0.05 to -0.00 mg/dl], p = 0.022). 주술기 부정맥, 수술 후 기계환기 시간, 중환자실 재원시간, 입원기간은 두 군에서 다르지 않았다. 29명의 환아를 대상으로 약동학을 분석하였고, 이구획 모델이 심폐우회술 중의 약동학을 가장 잘 설명할 수 있었다. 심폐우회술로 인해 중심구획이 증가하였지만, 덱스메데토미딘의 청소율은 심폐우회술에 영향을 받지 않았다. 10kg의 환아로 시뮬레이션 하였을 때, 심폐우회술 중의 혈장 농도 감소는 뚜렷하지 않았다.

고찰: 선천성 심장질환으로 수술을 받는 소아에서, 덱스메데토미딘은 주술기 급성 신손상의 빈도를 감소시키지 않았다. 심폐우회술을 이용한 심장 수술을 받는 소아에서 덱스메데토미딘은 심폐우회술 시작시에 용량을 증가하거나, 추가 주입없이 혈장 농도를 유지하며 사용할 수 있다.

주요어: 급성 신손상, 심장 수술, 덱스메데토미딘, 소아

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