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Original Article

Correlation between fluid overload and acute kidney injury after congenital cardiac surgery in infants

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Abstract: Objective: To analyze the correlation between fluid overload (FO) and postoperative acute kidney injury (AKI) and the effect of FO on clinical outcomes in infants undergoing congenital cardiac surgery (CCS). Methods: From January 2014 to December 2015, 94 infants admitted to the Department of Cardiothoracic Surgery in our hospital to undergo CCS under combined endotracheal intubation and intravenous anesthesia were enrolled as participants in this study. The infants were subdivided into the acute kidney injury group (AKI group) and the no acute kidney injury group (N-AKI group) in terms of the presence/absence of postoperative AKI. The preoperative, intraoperative and postoperative relevant risk factors were pooled and compared between the two groups. A multivariate logistic regression model was utilized to analyze the correlations of postoperative FO at 2 days and other potential risk factors with postoperative AKI and to examine the links of FO to the severity of AKI and adverse clinical outcomes. Results: Young age, postoperative serum creatinine level, CBP duration and postoperative cumulative FO at 2 days were independent risk factors for AKI after pediatric CCS, with receptive adjusted OR of 2.74 (95% CI: 2.32-3.01), 1.02 (95% CI: 1.01-1.03), 2.05 (95% CI: 1.65-2.49), and 1.98 (95% CI: 1.57-2.39). Length of hospital stay, the duration of ICU stay and mechanical ventilation time of the infants with FO were significantly longer than those without FO (All $P<0.05$). Additionally, FO was associated with the severity of AKI, with more severe AKI in infants with FO ($P=0.028$). Conclusions: FO is an independent risk factor for postoperative AKI after pediatric CCS and associated with postoperative adverse outcomes.

Keywords: Infant, congenital heart disease, fluid overload, acute kidney injury

Introduction

Pediatric congenital heart disease (CHD) is the heart disease occurring most often in children, and a primary cause of death in infants and of disability in children. It is reported approximately 0.7%-2.2% of CHD has been confirmed in China [1, 2]. Early surgical intervention is one of the major treatment methods for CHD. With the development of medical technology, the rate of long-term survival in CHD infants has enjoyed significant improvement [3, 4]. Due to the immaturity of renal development in infants, acute kidney injury (AKI) is a common severe complication in infants undergoing cardiopulmonary bypass (CPB) for CHD, with the mobility of 28%-52% [5, 6]. Previous studies have indicated that a variety of preoperative, intraoperative and postoperative factors including young age, CPB duration, low preoperative hemoglobin level, low weight and operation complexity increase the risk for postoperative AKI in infants undergoing congenital cardiac surgery (CCS) [5, 7-9].

The fluid management following CHD surgery is crucial to the recovery of infants [10]. Early adequate volume resuscitation can reverse organ hypoperfusion and improve prognosis, but the CPB surgery for CHD can cause hemodilution and capillary leakage, causing tissue edema. Since infants are poor at regulating fluid balance, postoperative fluid resuscitation may increase fluid load and reduce renal tissue perfusion. Additionally, retention of sodium may be exacerbated by stimulation of the renal renin-angiotensin-aldosterone system, so FO is common after pediatric CCS [11-13]. It is reported that FO is an independent risk factor for AKI and adverse clinical outcomes in critically ill patients and infants undergoing CCS, but the results are inconsistent [14-16]. The current study was designed to explore the correlation of FO with postoperative AKI after CCS and the effect of FO on clinical outcomes in infants.

Materials and methods

Participants

This study obtained approval from the Hospital Ethics Committee. From January 2014 to December 2015, a total of 94 infants undergoing CCS under combined endotracheal intubation and intravenous anesthesia in the Department of Cardiothoracic Surgery of our hospital were recruited in this study. Patients who were younger than 6 years old were eligible for enrollment if they had normal preoperative renal function, no use of mechanical ventilation, cardiac inotropes or additional auxiliary measures and complete postoperative follow-up data. Patients were excluded if he or she met any of the following criteria: emergency surgery, preoperative renal injury or use of preoperative cardiac inotropes. Of the eligible 94 infants, atrial/ventricular septal defect was present in 27 infants, atrial/ventricular septal defect with patent ductus arteriosus in 20 infants, atrial/ventricular septal defect with atrioventricular insufficiency in 19 infants, tetralogy of Fallot in 11 infants, patent ductus arteriosus with aortic stenosis in 10 infants, double outlet of right ventricle in 5 infants, completely pulmonary venous drainage in 1 infant, pulmonary stenosis in 1 infant and interrupted aortic arch in 1 infant.

Data collection

The following information were pooled retrospectively: general data, including sex, age and body height; preoperative data, including clinical diagnosis, presence or absence of cyanosis, the serum creatinine level, the urea nitrogen level, the cystatin C level and creatinine clearance rate; intraoperative factors, including risk adjustment classification for congenital heart Surgery-1 (RACHS-1), which is a classification system used for comparing surgical difficulty and risks based on the complexity of congenital heart defects. The risk adjustment was categorized into six levels, with higher level indicating greater surgical difficulty [17]. Addition intraoperative factors included CPB time, aortic clamping time and presence/absence of delayed sternal closure; postoperative factors, including the postoperative creatinine and cystatin C levels, presence/absence of cardiac arrhythmia and presence/absence of FO. FO is cumulative overload of the daily FO, for which the calculating formula states: Daily overload fluid (%) = [fluid input - fluid output)/preoperative weight] * 100% [18]. FO was defined as FO greater than or equal to 5% on day 2 after operation [15].

The diagnosis of AKI was performed according to the pRIFLE criteria. AKI was defined as the condition when the creatinine clearance rate of a child was decreased by over 25% within the first 48 hours postoperatively or persistent urine volume was less than 0.5 mL/kg/h for more than 8 hours. In terms of decrease in creatinine clearance and urine volume, AKI was classified into the following spectrum of progressive kidney injury: risk, injury, failure, loss and end-stage [19].

The clinical outcome measures of the patients included hospital stay, ICU stay duration, mechanical ventilation time and AKI classification.

Statistical analysis

The data analyses were performed with the use of the SPSS statistical software, version 19. Continuous variables were represented as mean ± standard deviation. The two-tailed chi-square tests or Fisher's exact tests were utilized for comparisons of categorical variables (composition ratio) between infants with postoperative AKI and those without during the study and the correlation between FO and the severity of AKI (classification); the two samples independent t-test was applied for comparing the mean continuous variables. A multivariate logistic regression model was applied to analyze the link of FO and other risk factors to postoperative AKI at 2 days postoperatively. Variables with statistical significance of less than 0.1 in the univariate analysis were further assessed with the multivariate logistic regression model. In the multivariate analysis, a probability likelihood ratio test was conducted on a basis of the maximum partial likelihood, and independent variables were screened by stepwise logistic regression. The statistical significance was set at α=0.05 using two-sided tests.

Table 1. General data and other preoperative characteristics of patients

Characteristic	N-AKI (n=63)	AKI (n=31)	t/χ²	P
Age (mon)	63.6±38.6	42.7±27.8	2.69	0.009
Age subgroup (mon)			4.78	0.029
<36	18 (28.6)	16 (51.6)		
≥36	45 (71.4)	15 (48.4)		
Sex			0.653	0.419
Male	32 (50.8)	13 (41.9)		
Female	31 (49.2)	18 (58.1)		
Weight (kg)	36.2±8.5	32.1±8.3	2.215	0.029
Cyanosis			4.742	0.030
No	56 (88.9)	22 (71.0)		
Yes	7 (11.1)	9 (29.0)		
Preoperative serum creatinine (μmol/L)	29.9±7.5	25.8±6.4	2.610	0.011
Preoperative urea nitrogen (mmol/L)	4.75±2.1	4.41±1.9	0.761	0.449
Preoperative cystatin C (mg/L)	1.79±0.60	1.54±0.46	2.041	0.044
Preoperative serum creatinine (mL/min/1.73 m²)	135.2±41.6	126.2±30.9	1.179	0.242

Table 2. Comparison of intraoperative factors between the two groups

Factor	N-AKI (n=63)	AKI (n=31)	t/χ²	P
RACHS-1 score (%)				0.169*
≤2	58 (92.1)	25 (80.6)		
>2	5 (7.9)	6 (19.4)		
Cardiopulmonary bypass (min)	105±23	124±29	3.448	0.001
Aortic clamping (min)	65±32	83±39	2.226	0.028
Delayed sternal closure (%)				0.106*
No	63 (100)	29 (93.5)		
Yes	0 (0)	2 (6.5)		

Note: *Fisher's exact test.

Results

During the study period, 31 (33%) of 94 infants underwent CCS with the use of CPB had postoperative AKI. **Table 1** shows the individual and preoperative characteristics of the infants in both the AKI group and the N-AKI group. No marked differences were noted in sex, preoperative urea nitrogen and creatinine clearance rate between the two groups. Among the infants in the AKI group, 51.6% were younger than 36 months old, 29% had cyanosis, which were considerably higher than those (28.6% and 11.1% respectively) of the N-AKI group (P=0.029 and 0.030, respecitvely). In addition, body weight, preoperative serum creatinine and cystatin C levels in the AKI group were strikingly lower than those in the N-AKI group (All P<0.05).

Comparisons of intraoperative and postoperative characteristics between the AKI group and the N-AKI group are shown in **Tables 2** and **3** respectively. Amongst the intraoperative factors, the CPB duration and aortic clamping time in the AKI group (105 min and 65 min respectively) were substantially longer than those of the N-AKI group (P=0.001 and 0.028, respectively). Nevertheless, the two groups differed slightly in RACHS-1 score and presence/absence of delayed sternal closure. In the postoperative factors, the incidence of postoperative arrhythmias was basically balanced in the two groups, but striking higher postoperative serum creatinine and cystatin C levels (32.7±7.8 μmol/L and 1.48±0.57 mg/L, respectively) were observed in the AKI group as compared with the N-AKI group (Both P<0.05). The proportion of infants with FO (48.4%) at 2 days postoperatively in the AKI group was substantially higher than that in the N-AKI group (P=0.006). **Figure 1** shows the cumulative FO at 1-5 days postoperatively in both groups, with markedly higher FO at 2-3 days in the AKI group (P<0.001).

Tables 1-3 indicate that age, body weight, presence/absence cyanosis, preoperative serum creatinine and cystatin C levels, CPB duration,

Table 3. Comparison of postoperative factors between the two groups

Factor	N-AKI (n=63)	AKI (n=31)	t/χ^2	P
Postoperative serum creatinine (μmol/L)	28.5±6.9	32.7±7.8	2.657	0.01
Postoperative cystatin C (mg/L)	1.04±0.52	1.48±0.57	3.736	<0.001
Postoperative arrhythmias			2.909	0.088
No	42 (66.7)	15 (48.4)		
Yes	21 (33.3)	16 (51.6)		
Cumulative FO at 2 days			7.651	0.006
No	50 (79.4)	16 (51.6)		
Yes	13 (20.6)	15 (48.4)		

Note: *Fisher's exact test.

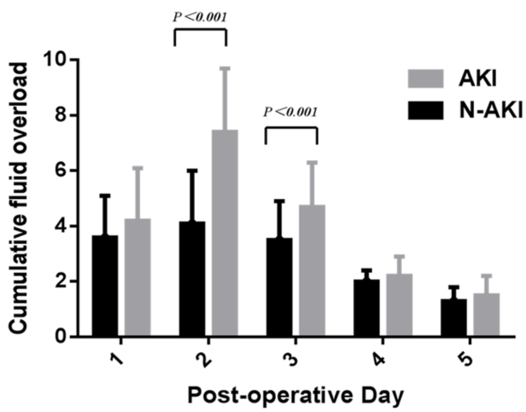

Figure 1. Comparison of postoperative cumulative FO between the AKI group and the N-AKI group. The values of FO at 1-5 days postoperatively in the N-AKI group were 3.6±1.5, 4.1±1.9, 3.5±1.4, 2.0±0.4, and 1.3±0.5, respectively; the values of FO at 1-5 days postoperatively in the AKI group were 4.2±1.9, 7.4±2.3, 4.7±1.6, 2.2±0.7, and 1.5±0.7, respectively. The values of FO at 2 and 3 days were considerably higher in the AKI group than in the N-AKI group (P<0.001).

aortic clamping time, postoperative serum creatinine and cystatin C level, and cumulative FO at 2 days postoperatively were all potential risk factors for postoperative AKI after pediatric CCS. The above-mentioned factors were further evaluated in a logistic regression analysis, showing that young age, the preoperative serum creatinine level, CBP time, postoperative cumulative FO at 2 days were independent risk factors for AKI after pediatric CCS. The adjusted OR were 2.74 (95% CI: 2.32-3.01), 1.02 (95% CI: 1.01-1.03), 2.05 (95% CI: 1.65-2.49) and 1.98 (95% CI: 1.57-2.39) respectively (**Table 4**).

Some of the clinical outcomes of infants were compared in terms of the presence/absence of cumulative FO at 2 days postoperatively (**Table 5**). The results showed that length of hospital stay, ICU retention duration, mechanical ventilation time of the infants with FO were markedly longer than those without FO (All P<0.05). Additionally, FO was also associated with postoperative AKI classification, and AKI was more severe in infants with FO (P=0.028).

Discussion

The incidence of AKI following CCS and the rate of perioperative adverse outcomes were considerably higher in infants than in adults because kidneys and other organs of infants are not well-developed, and their physiology, anatomy and extracorporeal circulation of the kidney are also different from those of adults [20, 21]. Therefore, it is of great significance to examine the risk factors of AKI after pediatric CCS for lowering the incidences of AKI and adverse clinical outcomes in infants.

FO is a common comorbidity in critically ill patients. Excessive fluid resuscitation leads to tissue edema and exacerbation of organ failure, resulting in AKI by multiple mechanisms [22]. In a multicenter study in China, FO considerably increased the incidence of AKI in critically ill adults (OR=4.508, 95% CI: 2.90-7.01) [23]. Studies have found that FO is also an independent risk factor for AKI in infants undergoing CCS. In a study from the USA, infants with FO were found to predispose to the development of AKI, and FO mostly occurred before the presence of AKI which was not associated with fluid accumulation [15]. In another study from China, as compared with the infants in whom postoperative FO occurred at 2 days, those who underwent CCS in whom FO was not present had lower incidence of postoperative AKI, which was reduced by 76% [24]. In the current study, the multivariate analysis showed that the presence of postoperative FO at 2 days significantly increased the risk of AKI, which was similar to the results of the above-mentioned studies. Nevertheless, according to another

Table 4. Risk factors for AKI after CCS in multivariate logistic regression analysis

Characteristic	Adjusted OR*	95% CI	P
Age		2.32-3.01	<0.001
≥36	1		
<36	2.74		
Postoperative serum creatinine (μmol/L)	1.02	1.01-1.03	0.020
CBP duration (min)		1.65-2.49	0.001
<90	1		
≥90	2.05		
Cumulative FO at 2 days		1.57-2.39	0.001
No	1		
Yes	1.98		

Note: *OR, odds ratio.

Table 5. Effect of cumulative FO on clinical outcomes

Outcome	Cumulative FO at 2 days		t/χ^2	P
	<5%	≥5%		
Length of hospital stay	12±4	15±6	2.727	0.008
ICU stay duration	78±20	90±21	2.550	0.013
Mechanical ventilation (d)			5.402	0.020
≤2	53 (80.3)	16 (57.1)		
>2	13 (19.7)	12 (42.9)		
AKI classification				0.028*
No	51 (77.3)	16 (57.1)		
Risk	8 (12.1)	5 (17.9)		
Injury	7 (10.6)	4 (14.3)		
Failure	0 (0)	3 (10.7)		

Note: *Fisher's exact test.

retrospective study, FO was not an independent risk factor for AKI after CCS in neonates and infants [7]. Currently, a variety of factors including the diagnostic criteria of AKI, the definition of FO, the age of infants, and the influence of confounding factors may be associated with the inconsistent findings regarding the correlation between FO and AKI after pediatric CCS. For example, in the current study, the diagnosis of AKI was based on the pRIFLE criteria, whereas in other studies the AKIN diagnostic criteria or the KDIGO clinical guideline were used [25, 26]. The three criteria have their unique advantages and disadvantages, with higher sensitivity of the pRIFLE criteria and higher specificity of the AKIN diagnostic criteria [27]. There is no uniform definition of FO after pediatric CCS. In the current study, the FO level reached the peak at 2 days postoperatively no matter AKI was present in infants undergoing CCS (**Figure 1**) or not. Moreover, FO at 2 days postoperatively has demonstrated to be significantly correlated with adverse clinical outcomes, so the criterion was set as postoperative FO no less than 5% at 2 days. In contrast, in other studies, FO ranging from 10-20% or FO at 1 day postoperatively was defined as the criterion [13, 15]. In addition, the current study is retrospective, so it is difficult to validate the causality between FO and AKI after CCS in a chronological order. In fact, the causality between them remains unknown [28].

In the current study, young age, elevated postoperative creatinine level and long CBP duration were also independent risk factors for AKI after pediatric CCS, which are similar to the results of other studies [29]. A multicenter prospective study revealed that CBP duration was linearly related to the risk of AKI after CCS, with longer CCS indicating higher risk [5]. In addition, the RACHS-1 classification and preoperative cyanosis have also been proved to be risk factors for AKI after CCS [30]. However, in the current study, no significant correlation was seen between the two factors. Therefore, additional studies are needed for further validation.

In addition, in the current study, markedly longer hospital stay, ICU stay and mechanical ventilation and more severe AKI in infants with FO at 2 days postoperatively suggest that the clinical outcomes of infants with FO are worse, which was also validated by the results of other studies [13, 15, 24]. Therefore, for infants at high risk of congenital heart disease, the management of postoperative fluid is essential and more efforts should be made to prevent the occurrence of postoperative FO.

In conclusion, the current study indicated that FO was an independent risk factor for AKI after pediatric CCS and correlated with various adverse outcomes. However, there are also some limitations in the current study, including a small sample size and a single center retrospective study by nature. In the future, multicenter and prospective studies with larger sample size are required to validate the correlation between FO and AKI after CCS. Additionally, more efforts should be made to improve the management of fluid to reduce postoperative adverse outcomes.

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Disclosure of conflict of interest

None.

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