PREVALENCE AND ASSOCIATED RISK FACTORS OF RENAL COMPLICATIONS IN CONGENITAL CARDIAC DISEASE PATIENTS

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ABSTRACT

Objective: To investigate the risk factors associated with renal complications and comparison of peritoneal dialysis survival and non-survival patients after open heart surgery.
Study Design: Descriptive cross-sectional study.
Place and Duration of Study: Pediatric cardiac anesthesia Department of Armed Forced Institute of Cardiology & National Institute of Heart Diseases from Jul 2017 to Jan 2018.
Material and Methods: Retrospective data was collected from hospital based registry. Demographics, clinical characteristics, complications and outcome of patients were recorded. Data analysis of 199 patients was done on SPSS version 22.
Results: Total of 199 patients were enrolled in the study, mean age was 4.9 ± 5 years (p=0.01), 117 (59.1%) were male and 82 (40.9%) were female patients. Out of total, 24 (12%) patients had kidney disease (KD) and underwent peritoneal dialysis (PD). Sixteen children (66.7%) died after PD while 08 children (33.3%) survived after PD. 09 (37.5%) had pulmonary edema (p<0.001), 05 (20.8%) had pulmonary hypertension (p=0.005), 09 (37.5%) had high inotropic duration (p=0.004) and 13(54.2%) patients had low cardiac output (p=0.001).
Conclusion: It was concluded that patients with renal impairment who underwent peritoneal dialysis had poor outcomes as they had longer hospital stay and high mortality rate. Risk factors associated with renal complications included pulmonary edema, high inotropic support, low cardiac output and pulmonary hypertension. Longitudinal follow-up studies with robust methodology are needed to fill significant knowledge gaps. There are currently no clear guidelines for clinicians in terms of renal assessment in the long term follow up after cardiac surgery in childhood.

Keywords: Acute kidney injury, Kidney Disease, Peritoneal Dialysis.

INTRODUCTION

With advances in care, children undergoing complex cardiac repairs are surviving more frequently, resulting in a markedly increasing number of adults with congenital heart disease[1,2]. It is important to think about the impact that these intensive interventions have on organ systems, including the kidney. The kidney is at high risk of long-term negative impact, given the pathophysiological changes that occur in the context of congenital heart disease, surgical intervention and cardiopulmonary bypass, post-operative critical care and recurrent exposure to potential renal insults[3]. Patients with congenital heart disease use substantial healthcare resources, and not just during the time of cardiac repair, but also as surviving adults with congenital heart disease[4]. Kidney disease (KD) also causes significant personal and economical health care burden and is associated with worse long term outcome, quality of life and well being in the general population[5]. Hence KD in patients with congenital heart disease has potential for synergistic negative impact. Although there are a significant gaps in the knowledge related to the renal outcomes of children with congenital heart disease and children who have had cardiac surgery, current evidence demonstrates KD as an increasingly prevalent and important problem in these patients[6]. RF was defined as a creatinine level of more than 1.2 mg/dL or oliguria (<0.5 mL/kg/hour) for more than 4 hours despite aggressive diuretic therapy and optimization of

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the inotropic support, or a combination of both[7]. Infants and children who undergo surgical repair of complex congenital heart diseases are more prone to develop renal dysfunction. The development of renal failure (RF) is a frequently reported complication after cardiopulmonary bypass surgery in infants and children. Studies have reported a high mortality rate ranging from 30-79%[7-8]. Fluid restrictions, diuretics, and inotropic agents have been the initial therapeutic strategies for mild renal dysfunction and low cardiac output syndrome. The more severe cases require a slow and continuous removal of the fluid by hemofiltration or peritoneal dialysis (PD)[9]. Compared with hemofiltration, PD in pediatric patients is associated with advantages in the establishment of vascular access, avoidance of systemic anticoagulation, and decreased associated risks of ischemic and embolic complications[10]. The feasibility and efficacy of PD, optimal timing of application, complications, prognosis, and predictive risk factors of the mortality in children undergoing PD after open heart surgery are currently under discussion[11]. We reviewed our experience with PD in treating children with RF after surgical repair of congenital heart disease. The aims of this study were:

- To determine the differences in clinical and laboratory variables between survivors and non-survivors receiving PD.
- To investigate the risk factors associated with prolonged peritoneal dialysis (PD) and the mortality of pediatric patients with renal failure after open heart surgery.

Given the potential to mitigate KD development and progression in many different populations, with universally accepted interventions, clinicians, researchers, and policy makers should be interested in this problem from both an economical and patient-centered outcome point of view.

MATERIAL AND METHODS

This was a descriptive cross-sectional study, conducted at paeds cardiac anaesthesia department. from, the medical records of 199 children that underwent open heart surgery at Pediatric surgery and anesthesia department of Armed Forced Institute of Cardiology & National Institute of Heart Diseases were reviewed retrospectively. Among them, 24 (12%) received PD. Study duration was from July 2017 to Jan 2018. The age, height, weight, diagnosis of the congenital heart disease, surgical procedure performed, cardiopulmonary bypass time, and aorta clamping duration were recorded. Serum sodium & potassium levels, serum creatinine levels, and daily urinary output were recorded before PD.

The indications for PD included: (1) hypervolemia with severe edema; (2) anuria or oliguria for more than 4 hours despite aggressive diuretic and inotropic support; (3) hyperkalemia (>5.5 mmol/L); (4) metabolic acidosis (serum pH <7.3, HCO3 < 18 mmol/L) persistent after failing to be corrected by at least two boluses of an intravenous sodium bicarbonate infusion and adjustment of the fluid status with an inotropic support; (5) low cardiac output with renal insufficiency. The PD catheter was connected to a closed system for peritoneal drainage. The dialysate solutions used were standard commercial preparations (Dianel PD-2; Baxter International Inc., Deerfield, IL, USA); heparin (500 U/L of dialysate) and potassium chloride were added. The dextrose concentration varied from 1.5−4.5%, and the choice of dextrose concentration depended on the presence of serum hyperglycemia. PD was started with a dwell volume from 10 mL to 20 mL/kg with a dwell time of 1-2 hours. The recovery of the urine output was defined as a urine output >1 mL/kg/hour, and the recovery of serum creatinine was defined as a decline in serum creatinine to preoperative levels. Indications for stopping PD included a return to a sufficient urine output, maintaining a negative fluid balance, and normalization of the serum electrolytes and acid-base status[12,13]. Serum creatinine at the day of surgery was extracted. For the patients who did not have laboratory

measurements on the day of surgery, measurements obtained within 3 days before procedure were taken as the baseline value. Renal function was estimated as glomerular filtration rate (GFR) by using the simplified modification of diet in renal disease equation (estimated glomerular filtration rate [eGFR] [ml/min/1.73 m^2] _ 186.3 _ [serum creatinine] _1.154 _ age_0.203 _ [0.742 if female])[5]. Estimated GFR values _200 ml/min/1.73 m^2 were set equal to 200 ml/min/1.73 m^2, according to Coresh et al[14].

Data Analysis

Normality was assessed using the Shapiro-Wilk test. In normally distributed parameters, values are expressed as mean ± standard error and comparison between groups was performed using independent t-test. In non-normally distributed data, values are expressed as median and interquartile range and comparison of values was performed using the Mann–Whitney U test. The comparison of categorical values was assessed using the chi-squared test and for continuous variables, association was found by using independent sample t-test. The differences were evaluated using microsoft excel 2016 and SPSS version 22.

Table: Comparison of peritoneal dialysis groups (survival & non-survival).

Variables	Patients had Peritoneal Dialysis (PD) n		*p*-value
	Survived	Non-survived	
Gender			
Male	03	12	0.598
Female	02	04	
Disease			
VSD (ventrciular septal defect)	0	2	0.253
PDA (paternt ductus arterious)	0	1	
PS (pulmonary stenosis)	0	1	
TGA (transposition of the great arteries)	2	1	
TOF (tetralogy of fallot)	1	7	
ASD (Atrial septal defect)	0	1	
DORV (double outlet right ventricle)	1	0	
IAA (Interputed aortic arch)	0	1	
Tricuspid atresia	0	1	
PAVSD Repair	1	0	
CAVSD	0	1	
Type of surgery			
Open	1	5	0.464
Close	1	1	
Inotropic support			
Mild	2	3	0.108
Moderate	3	4	
high	0	8	
Inotrope duration:			
>72 hrs	1	7	0.415
<72 hrs	4	7	
Low cardiac output	2	10	0.611
Pulmonary hypertension	0	4	0.329
Cardiac failure	0	15	<0.001
Re-ventilated	0	10	0.033
Pulmonary edema	1	8	0.582

RESULTS

Total of 199 patients were enrolled in our study, out of which 24 (12%) patients had kidney disease (KD) and undergone peritoneal dialysis (PD). We divided the patients who underwent

PD into two groups depending on the outcome: group-I, sixteen children (66.7%) died after PD; group-II, 08 children (33.3%) survived after PD but there was not any significant difference found between the two groups except cardiac failure (p<0.001) and re-ventilated (p=0.033) as both groups were having the PD patients. Their outcome is mentioned in table.

In our study population mean age was 4.9 ± 5 years (p=0.01), 117 (59.1%) were male and 82 (40.9%) were female. When we compared the patients had renal complications 24(12%) with other 175 (88%) no renal complication group, significant difference was found as shown in figure. About 16(66.7%) patients expired (p<0.001), 09 (37.5%) had pulmonary edema (p<0.001), 05 (20.8%) patients had pulmonary hypertension (p=0.005), 09 (37.5%) had high inotropic duration (p=0.004), 13 (54.2%) patients had low cardiac output (p=0.001). PD patients had longer ICU stay (8.6 ± 6 days, p=0.007).

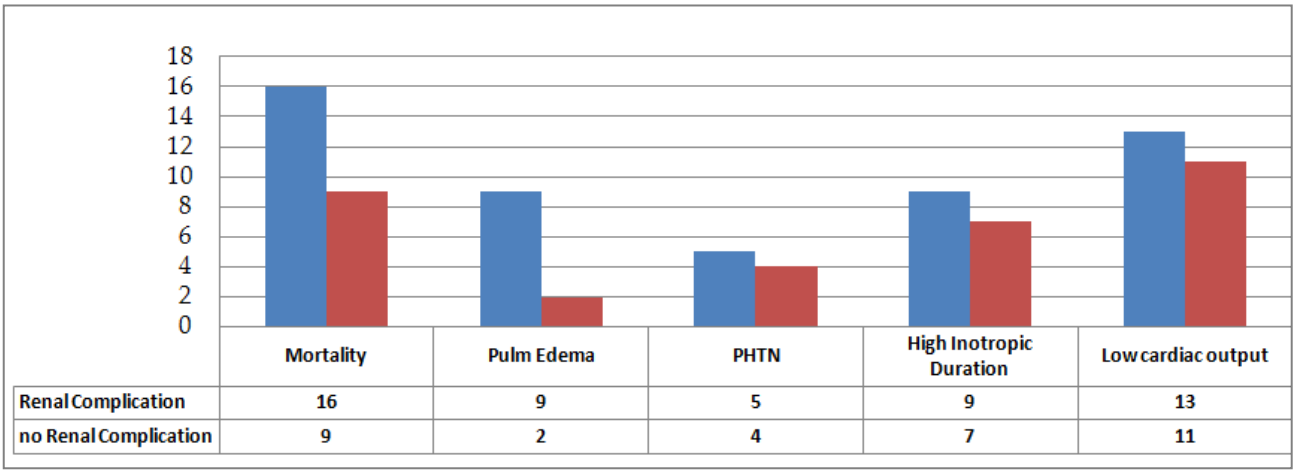

Figure: Comparison of patients who had renal complications and who do not had.

DISCUSSION

Pathophysiology in congenital heart disease can lead to long-term changes in kidney structure and function children with congenital heart disease have a number of risk factors for potential development of CKD later in life, including pathophysiological changes related to a structurally abnormal heart and circulation. These may include polycythemia, cyanosis and chronic hypoxia, changes in renal blood flow and intra glomerular hemodynamics, and derangements in neurohormonal activation. Several drugs used frequently in the setting of congenital heart disease have known nephrotoxicity[15]. In our study out of 199 patients, only 24 (12%) patients had renal dysfunction. A recent retrospective study of 206 hospitalized neonates with congenital heart disease demonstrated a significant decrease in renal function (estimated creatinine clearance) 42% of patients had AKI (with 70 % of these being classified as renal failure by modified pRIFLE criteria)[16]. In children, there is some retrospective data demonstrating AKI as a risk factor for CKD; Mammen et al, evaluated 126 critically ill children with AKI and demonstrated that at 1-3 years of follow-up, 10 % of children developed CKD (defined as estimated glomerular filtration rate (eGFR) <60 mL/ min/1.73 m^2 or persistent albuminuria)[16,17]. Forty-seven percent of children with a history of AKI were considered at risk of CKD (defined as eGFR of 60-90 mL/min/ 1.73 m^2, hyperfiltration (eGFR >150 mL/min/ 1.73 m^2), or hypertension)[17]. There are large, multicenter research studies currently underway, with primary aims of determining the risk of developing future KD. Long term follow up studies are also needed to predict the associated risk factors involved in developing kidney disease (KD) in congenital heart disease patients. A number of older, small studies have suggested

that renal dysfunction exists in adults with congenital heart disease. Aperia et al. demonstrated decreased GFR (by inulin clearance) in 5 out of 10 adults with tetralogy of fallot, a mean of 20 years post blalock-taussig shunt; mean GFR in these adults was 80 mls/min/1.73m^2[18]. In a renowned study, Flanagan et al. demonstrated a cohort of young adults (n 83) had proteinuria in one-third of cyanotic congenital heart disease patients. Risk of proteinuria was significantly higher than in an acyanotic control group with surgically corrected cyanotic congenital heart disease (Tetralogy of Fallot or transposition of the great vessels)[18,19] while in our study no significant difference was found between cyanotic and acyanotic groups, Reasons for differences between these groups were not explored in detail, particularly in relation to their early childhood course, prior surgical procedures, or concomitant medication use; however as expected, many patients with cyanotic congenital heart disease had more complex heart disease. Chronic glomerular injury as a prominent feature of cyanotic congenital heart disease has similarly been suggested by additional data demonstrating both an elevated albumin/creatinine ratio and an elevated protein/creatinine ratio in 38% (n=26) of long-standing cyanotic congenital heart disease[20]. In a small study of 43 children with cyanotic and acyanotic congenital heart disease, Agras et al, found a significant increase in the fractional excretion of sodium and N-acetyl-B-D-glucosaminidase (used as a marker of proximal tubular damage) in children with cyanotic congenital heart disease[21]. These markers of proximal tubular dysfunction and injury were also elevated in non-cyanotic congenital heart disease relative to controls, although to a lesser extent than in cyanotic congenital heart disease. A more recent study of 58 children with congenital heart disease (with healthy matched controls) confirmed similar findings[22] of note, in both of these studies, the majority of children in this study were in lower risk congenital heart surgery classes (by Risk Adjustment for Congenital Heart Surgery-1), the duration of follow-up was not specified, and it was not clear if urine evaluations occurred before or after cardiac repair. Recent data from a large, well designed study confirms the presence of CKD in patients with congenital heart disease[23]. When compared to the general population, the prevalence of significant renal impairment in another study was 18-fold higher in non-cyanotic and 35-fold higher in cyanotic congenital heart disease patients[23]. A study importantly demonstrated that it is not just those patients with cyanotic congenital heart disease that are at increased risk of CKD but also non-cyanotic, and changes occur fairly early in adulthood with a mean age at assessment of 36 ± 14 years[24]. KD contributes significantly to increase the risk of cardiovascular events and mortality in the general population which was 66.7% (p<0.001), there is not yet a clear understanding of the impact of KD in patients with congenital heart disease. A study demonstrates the young adults with congenital heart disease who have decreased GFR have lower survival than those with normal GFR. This is not simply because they have lower heart function; there is a clear additional effect of renal impairment over that of functional class and systemic ventricular function[22]. A population-based study in congenital heart disease patients surviving to >65 years demonstrated that one of the most powerful predictors of mortality was KD; the mortality risk associated with KD was larger than that associated with cancer, heart failure, myocardial infarction, or diabetes[25]. Children with pulmonary hypertension were at high risk of developing KD as it is demonstrated in other studies that endothelial dysfunction is present in KD, which is associated with pulmonary hypertension, left ventricle hyper-trophy, and increased cardiovascular disease events such as myocardial infarction[26-28]. We found it to be significant factor (p=0.005). The extent of vascular change is associated with the number of risk factors, their intensity, and exposure duration[29-31]. Thus, KD associated

cardiovascular disease pathogenesis in children appears to begin early in life with exposure to the atherogenic milieu of CKD, speaking to the potential importance of early KD detection and identifying risk factors of child KD development[32]. Given the large negative impact of KD on health outcomes in the general population and the child's potentially long life time to accumulate risk, KD development in children with congenital heart disease could place them at high risk for future cardiovascular disease. In addition, the presence of congenital heart disease concomitantly places patients at risk of exposure to factors that cause AKI, including cardiopulmonary bypass and nephrotoxins[15]. The risk of KD is higher with cyanotic congenital heart disease but it is also present with non cyanotic congenital heart disease. Many questions still need to be answered, yet this population represents one in whom long-term primary and secondary prevention strategies to reduce KD occurrence and KD progression could be instituted to significantly change outcomes. There should be an opportunity to mitigate KD progression and negative renal outcomes by instituting universally accepted interventions including stringent blood pressure control and its treatment. Ongoing generation, synthesis, and translation of evidence in this area are critically important, as the population of adult survivors of congenital heart disease expands. Patients with congenital heart disease should be recognized as a population at risk of developing KD. Although limited, the current epidemiological evidence suggests that renal dysfunction occur in patients with congenital heart disease with higher frequency than the general population and are detectable early in follow-up (i.e. during childhood). Despite a relatively young age, the best evidence suggests that approximately 30 to 50% of adult patients with congenital heart disease have significantly impaired renal function[1,16,20,32].

CONCLUSION

It was concluded that patients with renal impairment who underwent peritoneal dialysis had poor outcomes as they had longer hospital stay and high mortality rate. Risk factors associated with renal complications included pulmonary edema, high inotropic support, low cardiac output and pulmonary hypertension. Long-term studies with robust methodology are needed to fill significant gaps. There are currently no clear guidelines for clinicians in terms of renal assessment in the long term follow up after cardiac surgery in childhood.

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CONFLICT OF INTEREST

This study has no conflict of interest to be declare by any author.

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