RESEARCH PAPER

Profile of Acute Kidney Injury in Hospitalized Children with Idiopathic Nephrotic Syndrome

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Objective: To determine the incidence, risk factors and outcome of acute kidney injury (AKI) in hospitalized children with nephrotic syndrome. **Methods:** All consecutive hospitalized children (aged 1-14 years) with diagnosis of nephrotic syndrome between February 2016 and January 2017 were enrolled for the study. Children (aged 1-14 years) with features of nephritis, underlying secondary causes of nephrotic syndrome as well as children admitted for diagnostic renal biopsy and intravenous cyclophosphamide or rituximab infusion were excluded. **Results:** A total of 73 children (81 admissions) were enrolled; incidence of AKI was 16% (95% CI, 9-23). On multivariate logistic regression analysis, furosemide infusion was observed as an independent risk factor for acute kidney injury (OR 23; 95% CI, 3-141; P<0.001). Out of 13 children with AKI, three died. **Conclusions:** Acute kidney injury in hospitalized children with nephrotic syndrome has high risk of mortality. Children receiving furosemide infusion should be closely monitored for occurrence of acute kidney injury.

Keywords: *Furosemide, Outcome, Renal failure*.

Acute kidney injury (AKI) in childhood nephrotic syndrome is an uncommon but serious complication resulting from intravascular volume depletion, acute tubular necrosis, interstitial nephritis, bilateral renal venous thrombosis or rapid progression of underlying glomerular disease [1]. Sepsis, shock, peritonitis, severe hypoalbuminemia, nephrotoxic drugs exposure and steroid resistance are important risk factors for AKI in childhood nephrotic syndrome [2-5]. The published literature on AKI in hospitalized children with nephrotic syndrome has been limited to few case reports, secondary analysis of Healthcare Cost and Utilization Project- Kid's Inpatient Database (HCUP KID), and a multicenter retrospective study [4-7]. Due to the scant prospectively collected data on this aspect, we studied the incidence, risk factors and outcome of AKI in hospitalized children with nephrotic syndrome.

METHODS

This observational study was conducted at a tertiary-care pediatric hospital in Delhi from February 2016 to January 2017. All consecutive hospitalized children aged 1-14 years with diagnosis of nephrotic syndrome were screened. Nephrotic syndrome and associated complications were defined as per guidelines from Indian Pediatric Nephrology Group [8]. Children with nephrotic syndrome were admitted in presence of one or more of the following – anasarca, suspected major infections (peritonitis, pneumonia, cellulitis, meningitis *etc.*) or hypovolemic shock. Children with features of nephritis, underlying secondary causes of nephrotic syndrome as well as children admitted for diagnostic renal biopsy and infusion therapy (cyclophosphamide or rituximab) were excluded. The study was approved by Institutional Ethics Committee of Maulana Azad Medical College.

Based on a pilot study at our center, incidence of AKI in hospitalized children with nephrotic syndrome was estimated as 20%. The sample size at 95% confidence interval with 10% precision was calculated as 64.

Serum creatinine (SCr) was estimated by modified Jaffe's method standardized to isotope dilution mass spectrometry (IDMS) with instrument model Beckman Coulter AU400 and AU680. Diagnosis of AKI was made according to KDIGO clinical practice guideline of AKI using SCr criteria [9]. Any rise in SCr by 0.3 mg/dL within 48 hours or 1.5 times within next seven days from baseline value was labelled as AKI. Baseline SCr was defined as the most recent SCr value within last six months, including the day of admission. Patients with deranged SCr at admission were monitored daily for change in SCr level till two subsequent values became normal for age or static; whichever was earlier. Any fall in SCr by ≥0.3mg/dL within 48 hours or 1.5 times during next seven days from baseline was also labelled as AKI.

SCr was repeated every alternate day in children with normal SCr level at baseline till discharge. Those showing increase in SCr during hospitalization were subjected to daily estimation of SCr till normalization or discharge.

Clinical course of AKI was studied in terms of progression of AKI from one stage to another, requirement of dialysis and duration of hospitalization. Clinical outcome was measured in terms of renal recovery at discharge and mortality. Renal recovery at discharge was defined as 'complete' with normalization of SCr value and 'partial' with decrease in SCr level, but still higher for age [10]. Possible risk factors for AKI; like hypovolemia, infections, nephrotoxic drug exposure (ACE inhibitor, cyclosporine, vancomycin, amikacin, furosemide bolus and infusion) and steroid resistance were assesed.

Data were analyzed using SPSS version 23. Incidence of AKI was measured as a proportion of children developing AKI out of total episodes of hospitalizations with NS. Independent samples t test and Chi square or Fischer exact tests were used to test the significance of difference between two means and proportions, respectively. Mann-Whitney U test was used to test the significance of difference between two medians, where data were skewed. Risk factors for AKI were analyzed by univariate and multivariate logistic regression analysis.

RESULTS

A total of 124 admissions were assessed for enrollment, of which 43 were excluded (diagnostic renal biopsy=5; acute nephrotic syndrome=5; age <1 year=1; secondary nephrotic syndrome (HBV nephropathy)=1; IV Pulse Cyclophosphamide=27; and IV Rituximab=4). Finally, 73 children with 81 episodes of hospitalizations were enrolled; 67 children were admitted once, five were admitted twice and one child was admitted four times.

Baseline demographic, clinical and laboratory characteristics in children with and without AKI are shown in ***Table* I**. Indications for hospitalization included anasarca (45), peritonitis (9), cellulitis (6), pneumonia (5), gastroenteritis (4), hypovolemic shock (4), prolonged fever (2), meningitis (2), sepsis, varicella infection, hypertensive encephalopathy and arthritis (1 each). Fourteen children had histopathological diagnosis at the time of admission (12 minimal change disease and 2 focal segmental glomerulosclerosis).

The incidence of AKI in hospitalized children with NS was 16% (13/81) (95% CI, 9-23). Out of 13 AKI episodes; stage I, II and III were the first detected AKI stage in ten, two, and one children, respectively. Five out of 10 children with AKI stage I progressed to stage III. Finally, maximum AKI stage I, II and III were reached in five (38%), two (16%) and six (46%) children, respectively. All five children with maximum AKI stage I had complete renal recovery, whereas one each with stage II AKI had complete and partial renal recovery. Out of six children with maximum AKI stage III, one had complete renal recovery, two had partial recovery, and three died. Only one child with maximum AKI stage III received renal replacement therapy in the form of peritoneal dialysis. Median (IQR) time to develop AKI in hospitalized children with NS was 7 (4-11) days. Out of total 13 children with AKI; 7 (54%) recovered completely, 3 (23%) recovered partially and 3 (23%) died. Three out of 13 children with AKI underwent renal biopsy and reported

TABLE I FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN PATIENTS WITH NEPHROTIC SYNDROME (81 EPISODES)

Clinical Parameters	*AKI (n=13)*	*Non AKI (n=68)*	*P value*
*Age (y)	5 (3-7.6)	4.2 (3-8)	0.37
*Age of onset of NS (y)	3.3 (1.7-5)	3 (2-5.5)	0.76
*Duration of disease (y)	1 (0.6-3.1)	1 (0.5-1.9)	0.62
Male, *n* (%)	8 (61%)	37 (55%)	0.64
Clinical types of NS			
Initial episode	1 (8%)	21(32%)	0.10
IFRNS	1(8%)	14 (20%)	0.44
FRNS/SDNS	4 (30%)	22 (32%)	1
SRNS, *n* (%)	7 (54%)	11 (16%)	0.007
Peritonitis	4 (31%)	3 (4%)	0.001
Hypovolemic shock	4 (31%)	5 (7%)	0.003
Histopathology: MCD, *n* (%)	6 (46%)	7 (10%)	1
Death	3 (23%)	0	0.003
*Duration of hospital stay (*d*)	16 (12-24)	7 (5-9)	<0.001
Laboratory parameters			
S. Creatinine (mg/dL)	0.9 (0.7)	0.5 (0.1)	0.007
S. Albumin (g/dL)	1.5 (0.8)	1.5 (0.7)	0.64
Nephrotoxic drug, n (%)			
#Furosemide	12 (92%)	62 (91%)	1
CNI	3 (23%)	6 (9%)	0.13
ACE inhibitor	5 (38.5%)	9 (13%)	0.04
Amikacin	2 (15.4%)	4 (6%)	0.25
Vancomycin	3 (23%)	0 (0%)	0.003
$Furosemide infusion	9 (69%)	4 (6%)	<0.001

*NS: Nephrotic syndrome, CNI: calcineurin inhibitor, MCD: minimal change disease, IFRNS: infrequently relapsing NS, FRNS: frequently relapsing NS, SDNS: steroid dependent NS, SRNS: steroid resistant NS. All variables are expressed as mean (SD), except *median (IQR), #Oral or intermittent intravenous bolus, $Intravenous infusion.*

WHAT THIS STUDY ADDS?

- Acute kidney injury is common in hospitalized children with nephrotic syndrome and furosemide infusion is associated with an increased risk.

as minimal change disease with features of acute tubular necrosis and interstitial edema. Median duration of hospital stay was significantly higher in children with AKI in comparison to non-AKI (16 *vs.* 7 days, $P<0.001$).

On univariate logistic regression analysis, steroid resistance, hypovolemic shock, peritonitis, exposure with ACE inhibitor and furosemide infusion were associated with significantly increased risk of AKI (***Web Table* I**). On multivariate logistic regression analysis, furosemide infusion (OR 23; 95% CI, 3-141; $P<0.001$) was the only independent risk factor for AKI **(*Table* II)**.

DISCUSSION

In this prospective study incidence of AKI in hospitalized children with nephrotic syndrome was 16%, with majority reaching to AKI stage III. Furosemide infusion was an independent risk factor for AKI. Although, more than half of the children with AKI showed complete renal recovery at discharge, one fourth died during hospitalization.

Our finding on incidence of AKI was in line with HCUP-KID database analysis [4], where an increase in its incidence was noted from 3.3% in 2000 to 8.3% in 2009 in hospitalized children with NS. In contrast, a higher incidence of AKI (51% out of 636 hospitalizations) was reported from a North American study [7], which can be explained by use of more sensitive pRIFLE definition for AKI classification, in comparison to KDIGO definition used in our study. Six out of thirteen (46%) children in our study had AKI on admission, similar to an earlier report [7], suggesting intravascular hypovolemia at the time of presentation. Majority (54%); however, developed AKI later on, which could be due to nephrotoxic drug exposure during hospitalization. One third of children with AKI in our study had evidence of peritonitis, which was consistent with an earlier report, where peritonitis was a triggering event for AKI in 50% cases with nephrotic syndrome [11].

Children with AKI who underwent renal biopsy showed normal glomeruli with evidence of ATN and interstitial edema, similar to biopsy findings reported earlier [1,3]. Interstitial edema can result in decreased GFR by causing compression of renal tubules and thus increasing hydrostatic pressure in bowman's space [12]. Tubular obstruction by proteinaceous casts [13] and impaired glomerular permeability [14] are other mechanisms of AKI in NS.

A previous study showed that exposure to ACE inhibitor, calcineurin inhibitors and nephrotoxic antibiotics were associated with increased risk of AKI [7]. Proportion of children showing complete renal recovery was similar to study by Yassen, *et al*. [15]; however, mortality was higher. Majority of cases progressing to stage III AKI could be the reason for higher mortality in our study.

Our study had limitation of not using urine output criteria for diagnosis of AKI, which could have resulted in missing out few early stages AKI. This study was not powered to assess risk factors for AKI. We also did not calculate cumulative dose for injection furosemide, which was an independent risk factor for AKI in our study. Multicenter studies with larger sample size and longer follow-up to assess risk factors and outcomes for AKI in these children are needed.

To conclude, AKI is common in hospitalized children with NS, with significant mortality and morbidity. Children receiving furosemide infusion should be closely monitored for occurrence of AKI.

TABLE II MULTIVARIATE ANALYSIS OF RISK FACTORS FOR ACUTE KIDNEY INJURY IN CHILDREN WITH NEPHROTIC SYNDROME DURING HOSPITAL ADMISSION (N=73)

Parameters	*Odds ratio (95% CI)*
SRNS	4.9 (0.9-2.9)
Shock	6 (0.6-56)
Peritonitis	9.7 (0.7-127)
Furosemide infusion	23 (3-141)
ACE inhibitor	4 (0.5-38)

SRNS: steroid resistant nephrotic syndrome; ACE: Angiotensin convertase enzyme.

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