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A study of Acute Kidney Injury (AKI) in Neonatal Sepsis

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Abstract:
Objectives: *Neonatal sepsis is an important cause of morbidity and mortality especially among LBW and preterm babies. There is paucity of data on AKI in neonatal sepsis. The aim of the study was to evaluate the incidence of AKI in neonatal sepsis and delineate the risk factors associated with it.*
Methodology: *The prospective study was conducted from May 2006-June 2009 in NICU at SVPPGIP and S.C.B. Medical College. A total of 120 cases with neonatal septicemia without gross congenital anomaly of genitourinary tract were included in the study on the basis of either a positive sepsis screen and/or a positive blood culture. AKI was diagnosed based on serum creatinine level >1.5mg/dl. The demographic profile, clinical features, etiology, underlying risk factors and outcome were analyzed in the study.*
Results: *Out of 120 neonates 62% were male baby and with mean gestational age of 35.94weeks.16% (n=19) were VLBW and 46.2% (n=55) were LBW babies. AKI was found in 27.5 % (n=33) cases and majority of cases (n=26) were non-oliguric (urine output >1ml/kg/hour) with mean day of presentation was 1.36days. DIC and shock were present in 64% (n=21) out of 33 cases with AKI and 27.2% out of 87 (n=15) cases without AKI. Mortality was higher with non-oliguric AKI and the mean day of recovery was 4.31 days. Septic neonates with AKI were associated with higher mortality (54.5%) than those without AKI (24.1%).*
Conclusion: *AKI is a very common entity among septic neonates. LBW is an important risk factor and coexisting shock and DIC were significantly associated for the development of AKI. Majority of septic newborns develop AKI in the first two days and are non-oliguric. This stress the need for septic neonates to be screened for AKI.*
Key words: *Neonatal sepsis, Acute kidney injury, preterm babies.*

I. Introduction

Acute Kidney Injury (AKI) is characterized by a sudden impairment in renal function leading to inability of the kidneys to excrete nitrogenous waste. Even though the criteria for neonatal AKI vary among different studies, a consensus definition is based on serum creatinine level of >1.5mg/dl. The causes of neonatal AKI are multiple and can be divided into prerenal, renal and post-renal categories. Among these, prerenal azotemia is the most common type of AKI encountered in the neonates (85%).

Neonatal sepsis is the most important cause of morbidity and mortality especially among low birth weight (LBW) and preterm babies in developing countries[1]. According to the pooled hospital data based on NNPD survey, the incidence of neonatal sepsis is around 3.8%. The incidence of AKI in children appears to be increasing, and the etiology of AKI over the past decades has shifted from primary renal disease to multifactorial causes, particularly in hospitalized children. There is paucity of data on AKI in neonatal sepsis. Earlier studies have focused on perinatal asphyxia as the cause of AKI. The aim of the study was to evaluate the incidence of AKI in neonatal sepsis and delineate the risk factors associated with it.

II. Materials And Method

The prospective study was conducted from May 2006-June 2009 in newborn admitted with sepsis at SVPPGIP and S.C.B. Medical College, Cuttack. Sepsis was diagnosed on basis of either a positive sepsis screen and/or a positive blood culture in symptomatic neonates. Sepsis screen were considered positive if $\geq$ 2 of the 4 criteria were present, which includes: 1) C-Reactive Protein (CRP) >0.6mg/dl 2) Micro Erythrocyte Sedimentation Rate (ESR) > age in days + 2mm or > 15mm fall in 1st hour 3) leucopenia Total leukocyte count <5000/cmm with low absolute neutrophil count (< 2000cells/ cmm) and 4) Immature: total neutrophil ratio >0.2.CRP was measured by turbidimetric immunoassay. A total of 120 cases with neonatal septicemia without any gross congenital anomaly of genitourinary tract were included in the study on the basis of either a positive sepsis screen and/or a positive blood culture. AKI was diagnosed based on serum creatinine level >1.5mg/dl and Oliguria was defined as urine output <1ml/Kg/hr. The demographic profile, clinical features, etiology, underlying risk factors and outcome were analyzed in the study.

For the term and late preterm neonates, the diagnosis of AKI was made on the basis of serum creatinine levels >1.5 mg/dL at any time after first 48 hours of life with normal maternal serum creatinine levels, or

creatinine level that increased at the rate of 0.3 mg/dL per day 48 hours after birth with or without oligo or anuria.[2,3]Since the creatinine levels of preterm neonates (<34 weeks) were high in the first 3-5 days of life, serum levels were measured serially for 48 to 72 hours to diagnose AKI.[4] The assessment of oliguria and anuria was based on urine flow of <1 mL/kg per hour and <0.5 mL/kg per hour 48 hours after birth.[5,6] Urine output was measured every day by collecting urine in adhesive bags in an 8-hour interval. Glomerular filtration rate was estimated using Schwartz formula (k × height [cm]/plasma creatinine [mg/dL]). The constant k was 0.33 for infants born after gestation for less than 38 weeks and 0.45 for those born after gestation for more than or equal to 38 weeks.[7,8] Renal impairment was grouped into three categories based on the site involved: pre-renal, renal and post-renal AKI. Differentiation of pre-renal and renal failure was based on urine sodium and creatinine levels and fractional excretion of sodium (FENa). Premature rupture of membranes was defined as membrane rupture 18 hr before the onset of labor.[9] Asphyxia was diagnosed when patients met the following criteria: (1) metabolic or severe, combined acidemia (pH less than 7.0) in arterial umbilical cord blood; (2) Apgar score of 0-3 for more than 5 minutes; (3) neonatal neurological manifestations (seizures, coma or hypotonia); (4) multisystemic dysfunction of organs, i.e. cardiovascular, gastrointestinal, hematological, pulmonary or renal systems).[10] All neonates with clinical features of asphyxia were staged by the Sarnat and Sarnat scoring system.[11] Dehydration was defined as a weight loss of more than 10% of the birth weight at the end of the 1st week of life or clinical findings of dehydration with hypernatremia.[12] Respiratory distress syndrome was defined on the basis of clinical (downe score in term, Silverman Anderson score in preterm), laboratory (ABG showing respiratory acidosis), radiological findings (x-ray opacities) and respiratory support for ≥6 hours within the first 24 hours after birth. Sepsis was defined as a positive blood culture or urine culture along with clinical signs of infection.[13, 14] Metabolic acidosis was diagnosed if blood pH <7.20 and HCO3 ≤12 mmol/ L or base excess ≤ -6. Hypernatremia and hyponatremia were defined as serum sodium concentration >150 mmol/ L and <130 mmol/L, respectively.[12] Hyperkalemia was defined as serum potassium level >7.5 mmol/L in the first day of life and >6.5 mmol/L in the remaining days.[15] Hypertension was diagnosed with systolic and diastolic blood pressures curves described by Zubrow et al.[16] Liver failure was defined by the elevated levels of aspartate aminotransferase and alanine aminotransferase that were three times higher than upper limit normal values.

Data collection

Detailed maternal and neonatal information about age, gender, gestational age, prenatal history, maternal and neonatal medical diseases, Apgar score at five minutes, use of medical devices (central venous catheter, umbilical catheter, percutaneous catheter, mechanical ventilation), other relevant medical conditions and laboratory results, treatment modality and outcomes were collected for each infant.

Statistical analysis

Statistical analyses were performed by SPSS version 15 (SSPS Inc, Chicago, USA). Univariate analysis was performed to identify differences between infants with and without AKI; the Chi-square test and Fisher's exact test were used to compare categorical variables and Student's t test was used to analyze continuous variables. Significant variables were identified by univariate analysis and entered into a stepwise logistic regression analysis. A P value less than 0.05 was considered statistically significant.

III. Results

Out of 120 septic neonates 62% (n=74) were male baby. Mean gestational age of study cohort was 35.94weeks and 43.3% neonates were preterm. 16% (n=19) were VLBW and 46.2% (n=55) were LBW babies. Out of total number of blood culture positive cases (n=38), gram (-ve) organisms constituted 55.3% and gram (+ve) 44.7% cases. Out of gram(-ve) cases Klebsiella and E.Coli and gram(+ve) cases staphylococcus aurous and Group B streptococcus contributed to majority cases. Meningitis was associated with 33 cases(27.5%). AKI was found in 27.5 % (n=33) cases and majority of cases (n=26) were non-oliguric (urine output >1ml/kg/hour) with mean day of presentation was 1.36days and the mean day of recovery was 4.31 days. Metabolic acidosis, birth asphyxia, DIC and shock in septic neonates with AKI were significantly higher in comparison with septic neonates without AKI as shown in table 1. The differences between oliguric and non-oliguric including the mortality were not statistically significant as shown in Table-2. As expected the calculated GFR was low in case of AKI than in patients without AKI. Septic neonates with AKI were associated with higher mortality (54.5%) than those without AKI (24.1%) as shown in Table-1. The other risk factors of AKI like low birth weight, small for age babies, with history of prolonged rupture of membranes not showed any statistical significance

TABLE 1. Comparison of Septic neonates with and without AKI.

Parameters	With AKI (n=330	Without AKI (n=87)	p-value
Prolonged rupture of membranes	11 (33%)	32 (37%)	0.6
Mean gestational age(wk)	35.09±3.8	35.88±3.76	0.56
Term>37wks	17(52%)	52(60%)	0.5
Preterm<37wks	16(48%)	25(29%)	0.04
Mean Wt(gms)	2140+462.2	2190+496.4	0.08
Small for date babies	10 (30%)	32 (35%)	0.5
Early onset sepsis	7(21%)	17(19.5%)	0.4
Metabolic acidosis	28 (84%)	59 (68%)	0.03
Hyponatremia	20 (60%)	42 (48%)	0.06
Hyperkalemia	24(73%)	55 (63%)	0.07
Birth asphyxia	26 (78%)	47 (54%)	0.043
Respiratory distress syndrome	9 (27%)	26 (30%)	0.2
Meningitis	11 (33%)	22 (25%)	0.09
Liver failure	6 (18%)	21 (24%)	0.3
Culture positive	10(33%)	28(32%)	0.8
DIC/Shock	21(64%)	15(17%)	<0.005
Mortality	18(54.5%)	20(23%)	<0.005

TABLE 2. Comparison of Septic Neonates with Oliguric and Non-oliguric AKI.

Parameters	Oliguric-AKI (n=7)	Non-oliguric AKI (n=26)	p-value
Mean gestational age(wk)	34.25	36.48	0.083
Mean Wt(gm)	2100	2127	0.380
Mean day at presentation	7.27	8.36	0.706
Blood C/S(+ve)	4(62.5%)	7(26.9%)	0.175
Meningitis	2(28.5%)	9(34.6%)	0.303
Survival	1(14.5%)	15(58%)	0.06

IV. Discussion

In our study LBW (Birth weight <2500gm) constitute 60.2% and preterm 43.3% of the study group. Males are predominantly infected than females. LBW is an important risk factor for development of sepsis. Narang A et al reported LBW and prematurity are risk factors for sepsis in newborn in Indian study[20]. Blood culture was positive in around 1/3rd of cases and Gram (-ve) septicemia was slightly more prevalent (55.3%) in our set up. Out of 120 cases only 33 cases (less than 1/3) had proven meningitis. In our study, around 28% of neonates with sepsis had AKI (i.e. 33 cases out of 120 cases) which is similar to mathur study where he had 26% of septic neonates with AKI[17]. Age of presentation was 1.36 days and recovery was 4.31 days in comparison with mathur study mean duration of recovery was 5.5 days. We had only 21 % of AKI presented as oliguric AKI similar to mathur study, also 15% of AKI was oliguric[17]. No point of measuring the urine output as a diagnosing tool. The mean gestation of neonates with AKI was similar to those without AKI (35.09±3.8 vs 35.88±3.76, p = 0.56). In case of preterm due to immature kidneys under sepsis had a significant higher incidence of AKI, but not in case of the small for age babies. Mathur showed a significantly higher number of babies with ARF weighed less than 2500 gm[17]. He could not able to classify the birth weight in terms of gestational age. In mathur study, the association of meningitis disseminated intravascular coagulation (DIC) and shock was also significantly higher in neonates with AKI. We also had a significant difference in the DIC and shock, birth asphyxia and metabolic acidosis which were more common in septic neonates with AKI than without AKI, but no difference in meningitis. Sharon found that AKI (SCr >1.5 mg/dl) occurred in 20/33 (66%) of infants with severe asphyxia compared with 0/33 (0%) in those with moderate asphyxia.[18] Mortality in neonates who developed AKI was significantly higher similarly our study also had significantly higher mortality in patients with AKI. Other factors like gestational age, weight, H/o PROM, electrolyte disturbances, respiratory distress syndrome, liver failure, culture positivity were assessed, but no significant differences between septic neonates with AKI and without AKI. AKI had recovered only in 15 out of 33 septic neonates which is very similar to mathur study.[17] Previously, severe respiratory disease was often responsible for pre-renal AKI, but with improvements in management of this condition. Neonatal sepsis, perinatal asphyxia, Necrotizing enterocolitis and major surgeries have emerged as the common predisposing causes.

V. Conclusion

The present study clearly reveals that AKI is a very common entity among septic neonates and associated with high mortality. Prematurity is an important risk factor for the development of AKI in neonates with sepsis. Urine output is not criteria for the AKI. The latent period for the development of AKI in neonatal

sepsis is short. Coexisting shock and DIC were significantly associated with AKI. Early and repeated renal function tests to be done and treat accordingly will prevent the neonatal mortality and chronic kidney disease. Limitations: we could not able to assess the effect of the nephrotoxic antibiotics used.

Conflict of Interest: Nil

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