Acute Kidney Injury in Neonatal Sepsis in a Tertiary Care Hospital

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ABSTRACT

BACKGROUND

Sepsis remains as a leading cause of morbidity and mortality among neonates. The present study was undertaken with the objective of evaluating occurrence of AKI in neonatal sepsis using AKIN criteria, associated risk factors and outcome.

METHODS

The study was conducted in the NICU of Niloufer Hospital, Hyderabad, India. The present study is a retrospective cohort study. Medical records of 200 cases of neonates with sepsis admitted from October 2019 to March 2020 were studied. Neonatal sepsis was diagnosed on the basis of either a positive sepsis screen or a positive blood culture in symptomatic neonates. The sepsis screen was positive if 2 or more of the following were present - CRP >1 mg/dL; micro-ESR > age in days + 2 mm or > 15 mm fall in first hour; total leucocyte count 15000/mm^3, immature: total neutrophil ratio >0.2. Acute renal failure (ARF) was defined as per AKIN criteria.

RESULTS

13 out of 200 (6.5%) neonates with sepsis had AKI; 3 babies (23.07%) were in oliguric AKI and 10 (76.92%) babies were in non-oliguric AKI. The presence of shock and DIC was found to be a significant risk factor for AKI.

CONCLUSIONS

Incidence and mortality associated with AKI in sepsis was found to be 6.5% and 30.76% respectively. The high mortality among septicaemic neonates with AKI stresses the need for neonates-with-sepsis to be screened for renal failure, as early recognition of coexisting risk factors for AKI may reduce the risk of its occurrence and early intervention can lead to better outcome.

KEYWORDS

Acute Kidney Injury, Sepsis, AKIN Criteria, Shock, DIC

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BACKGROUND

Sepsis is the commonest cause of neonatal mortality. It accounts to 30 - 50% of the total neonatal deaths in the developing countries.[1,2] Sepsis affects many vital organs of the body leading to Multiple Organ Dysfunction Syndrome (MODS) of which kidney is one of the most important organs to be affected. Acute kidney injury (AKI) is characterized by sudden (within 48 hours) impairment in kidney function that results in the retention of nitrogenous waste products, e.g. urea and alters the regulation of ECF volume, electrolytes and acid base homeostasis. It affects 8-24% of critically ill neonates and has a mortality rate of 10 to 61%.[3] The common conditions contributing to kidney injury in neonates according to various studies are perinatal asphyxia, neonatal sepsis, respiratory distress syndrome, dehydration, heart failure, nephrotoxic drug medication and urological anomalies,with asphyxia and sepsis being the most common.[4-9]

Majority of the studies on renal failure in neonates were based on old definitions.[5,6] Most recent studies on renal injury using the AKIN definition are few in the entire pediatric age group, resulting in lack of knowledge regarding exact incidence of AKI in neonates not only in our country, but also in current world literature in general. The present study was undertaken with the objective of evaluating occurrence of AKI in neonatal sepsis using AKIN criteria, associated risk factors and outcome.

METHODS

This is a retrospective cohort study. Medical records of 200 neonates admitted with sepsis were studied. The study was conducted in the out born nursery of Niloufer hospital, a tertiary care teaching hospital at Hyderabad, India, during the period October 2019 to March 2020.

Inclusion and Exclusion Criteria

200 cases of neonatal sepsis admitted from October 2019 to March 2020 were included in the study. Neonates with single kidney, dysplastic kidney, hydronephrosis, cystic kidneys, and obstructive uropathy were excluded.

Study Variables

The study variables included gestational age, birth weight, sex, onset of sepsis, maternal risk factors, perinatal risk factors, associated risk factors-DIC, shock.

Study Procedure

Neonatal sepsis was diagnosed on the basis of either a positive sepsis screen or a positive blood culture in symptomatic neonates. The sepsis screen was positive if 2 or more of the following were present – CRP >1 mg/dL, micro- ESR >age in days+ 2 mm or >15 mm fall in first hour, Total leucocyte count 15000/mm^3, immature: total neutrophil ratio >0.2.[10-12] In our hospital CRP > 6 is considered positive. Serial serum creatinine, serum electrolytes, urinary electrolytes were sent.

On the basis of serum creatinine values of three consecutive days, all the neonates with suspected sepsis were evaluated for acute kidney injury. The presence of Acute Kidney Injury was classified based on the definition given by the Acute Kidney Injury Network (Table 1.) Differentiation of pre-renal and intrinsic renal failure was based on renal indices. (Table 2)[13]

Data Analysis

The data was entered into Microsoft excel sheet and analysed using Statistical package for Social Sciences (SPSS) Software version 16. The significance of relation between various parameters were analysed using chi square test and p value <0.05 was taken as statistically significant.

Ethical Consideration

The Institutional Ethics Committee permission was obtained. It was observed that informed written consent from parents for obtaining samples for investigations and treatment was documented in medical records which is done daily for every patient as per hospital policy.

RESULTS

Out of 200 neonates with evidence of sepsis enrolled into the study, AKI was diagnosed in 13 babies (6.5%). In this study, 2 out 13 babies who developed AKI were preterm i.e., 15.38% where as 84.62% i.e., 11 out of 13 babies with AKI were of term gestation. It was found that out of 13 babies with AKI, 5 babies (38.46%) were of Birth weight <2500 gms and 8 (61.54%) babies were of Birth weight >2500 gms. There was no statistically significant relationship with respect to gestational age, birth weight and AKI. (p=0.54). The proportion of AKI in neonates with sepsis was slightly more in males i.e., 8 out of 13 which was statistically not significant.

It was observed that, EOS was found in 8(71.54%) out of 13 babies with AKI and LOS was seen in 5 (38.46%) babies with AKI which was statistically not significant. This suggests that the risk of developing AKI did not differ significantly in relation to the onset of sepsis in newborns. Various Maternal risk factors like Febrile illness 2 weeks prior to delivery, ingestion of drugs like NSAIDS, ACE inhibitors and perinatal risk factors during labour like meconium stained liquor, foul smelling liquor, prolonged rupture of membranes for >24 hrs, difficult labour with instrumentation were analysed . Out of 13 babies with sepsis who developed AKI, 3 (23.07%) babies were born to mothers with prolonged rupture of membranes, 2 (15.38%) babies were born to mothers with meconium stained liquor and only one (7.69%) was born to mother with difficult labour with

instrumentation. The association between risk factors during labour and the development of AKI was not statistically significant. About 4 (30.77%) out of 13 babies with AKI had a positive blood culture.

The commonest organism isolated in our study in those with AKI was Klebsiella (23.07%) followed by E. coli (7.69%). Out of 13 babies with AKI, none of the babies had coexistent Meningitis. Out of 200 neonates with sepsis, DIC was found in 8 babies and Shock was found in 14 babies. Out 13 babies with AKI, 02 (15.38%) had DIC and 3 (23.07%) had shock as a predisposing condition respectively. (Table 3) Thus DIC and shock were significantly associated with development of AKI. ($p<0.05$)

Stages of AKI

As per AKIN criteria, 7 (53.84%) cases were found to be in AKI Stage 1, 2 (15.38%) cases in AKI Stage 2 and 4 (30.77%) cases were found to be in AKI Stage 3. (Figure 1)

In our study, it was found that out of 13 babies with AKI, 3 babies were in oliguric AKI and 10 babies were in non-oliguric AKI. 11 (84.61%) out of 13 babies had intrinsic renal failure and 2 babies (15.38%) had prerenal failure. Majority of the babies with both nonoliguric and oliguric AKI were detected in stage 1. This study suggests that AKI can be detected at an early stage by measuring serial serum creatinine by using AKIN criteria.

In our study, 9 (69.24%) out of 13 babies with AKI survived and 4 (30.76%) out of 13 babies died. This shows that septicaemic babies with AKI had higher mortality than those without AKI. The relation between the mortality and AKI was statistically significant. ($p<0.05$). (Table 4). It was found that the mortality was higher in babies who were in Stage 3. Out of 3 neonates with Oliguric AKI, 2 babies (66%) survived and one baby (33%) died. In non-oliguric AKI, out of 10 neonates, 8 babies (70%) survived and 2 babies (30%) died. Hence, the mortality rates in babies with oliguric and non-oliguric AKI did not differ significantly. Neonates with prerenal AKI were managed with adequate fluids. Those with intrinsic AKI were managed with fluid restriction, correction of electrolyte abnormalities and inotrope support for neonates in shock. One baby with Oliguric AKI needed dialysis and the baby did not survive. All those Neonates with AKI who survived had normal renal functions with recovery time of two weeks.

$$\text{Renal Failure Index} = \frac{\text{Urinary Na x plasma creatinine}}{\text{Urine Creatinine}} \text{x } 100$$

$$\text{Fractional Excretion of Sodium (FENa)} = \frac{\text{Urinary Na x plasma creatinine}}{\text{Plasma sodium x Urine Creatinine}} \text{x } 100$$

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine of at least 0.3 mg/dL or Increase of more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine of more than to 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	Increase in serum creatinine of more than 300% (> 3-fold) from baseline or serum creatinine of more than or equal to 4 mg/dL with an acute rise of 0.5 mg/dL	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours

Table 1. AKIN Criteria for AKI

Parameters	Prerenal	Intrinsic
Urinary Na	< 20 meq/L	>50 meq/L
Renal Failure Index	Low < 1	High >4
Fractional Excretion of Na	</= 1	>3

Table 2. Parameters to Differentiate Prerenal and Intrinsic Kidney Injury

	AKI	Without AKI	Chi², P Value
DIC	2 (15.38%)	6 (3.20%)	4.66, 0.03
SHOCK	3 (23.07%)	11 (5.88%)	5.49,0.02

Table 3. Association of DIC and Shock with AKI

	AKI	Without AKI	Chi², P Value
Mortality	4 (30.76%)	8 (4.27%)	5.49, 0.0001
Recovered	9 (69.24%)	179 (95.73%)	

Table 4. Outcome in Neonatal Sepsis

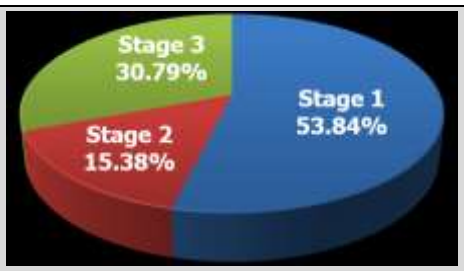

Figure 1. Distribution of AKI in Relation to Stages

DISCUSSION

Sepsis is one of the important predisposing causes of renal injury. In our study, out of 200 neonates with sepsis, 6.5% of cases developed acute kidney injury which was not comparable to any of the studies. This difference can be attributed to the fact that the diagnosis of AKI in the present study is done using the currently accepted AKIN definition (based on rising values of serum creatinine) Whereas in other studies conducted by Mathur et al[5] AKI was diagnosed based on blood urea levels. Although in a study by S. K. Pradhan et al[14] diagnosis was based on serum creatinine >1.5 mg/dL, the incidence was high due to small sample size. Jayashree et al[6] and Agras et al[7] reported 15% and 3.4% of neonates with sepsis had AKI respectively.

AKI was not found to be significantly different among term and preterm neonates in our study which was comparable with the result of the study by Mathur et al.[5] This suggests that neonates at all gestations are at an equal risk of AKI in sepsis. However in study by S. K. Pradhan et al[14] it was found that Prematurity is an important risk factor for the development of AKI in neonates with sepsis which was probably due to higher proportion of preterms in the study. Mortazavi et al,[8] who reported that pre-term cases

were less frequently accompanied by AKI (25.2%) than those who were full-term (70.2%).

In our study, the incidence of AKI did not differ significantly in terms of low birth weight. S. K. Pradhan et al[14] reported AKI in 30% low birth weight, although this finding was statistically not significant. In contrary, Mathur[5] et al showed that low birth weight (86.5%) was significantly associated with AKI.[5] In our study, the incidence of neonatal sepsis was high in males, the occurrence of AKI did not differ significantly with respect to sex in our study. This finding was comparable with the finding of studies by Mathur et al[5] and S.K. Pradhan et al.[14] There was no significant association found between the onset of sepsis (EOS/ LOS) and development of AKI in the present study which was comparable with studies by Mathur et al[5] and S. K. Pradhan et al.[14] Various Maternal risk factors like Febrile illness 2 weeks prior to delivery, ingestion of drugs like NSAIDS, ACE inhibitors and perinatal risk factors during labour like meconium stained liquor, foul smelling liquor, prolonged rupture of membranes, difficult instrumentation during labour did not differ significantly in septicaemic neonates with AKI and those without AKI in the present study similar to other studies by Mathur et al,[5] S. K. Pradhan et al.[14]

In the present study, blood culture positivity was present in 30.77% of neonates with AKI. Out of 200 neonates with sepsis, the most common organisms isolated in neonates with sepsis associated with or without AKI were Klebsiella (23.07% & 28.88% respectively) followed by E. coli (7.69% & 2.67% respectively), similar to results in study by S. K. Pradhan et al.[14] Blood culture positivity was not found to be significantly different between the neonates with AKI and without AKI and this was found to be similar to study Mathur et al[5] and S. K. Pradhan et al.[14]

In the present study, none of the neonates with AKI had meningitis and significant association could not be found which was not comparable with the study by Mathur et al[5] which showed significant association between meningitis and AKI. (p=0.01). The reason for significant association can be because meningitis can lead to multi-organ dysfunction with kidney being most commonly affected.

The presence of coexisting conditions like DIC and Shock were found to be significantly associated with the development of AKI (p<0.05). These results were comparable with the findings of studies by Mathur et al[5] (p<0.001) and S. K. Pradhan et al[14] (p<0.00). Jayashree et al[6] reported 66.6% of neonates with AKI had shock.

Although AKI in neonates has been reported to be predominantly oliguric, it was observed that AKI secondary to neonatal sepsis was predominantly nonoliguric. (76.9%). This observation was comparable with studies by S.K. Pradhan et al,[14] Mathur et al[5] and Doronjski et al[9] reported nonoliguric AKI in 80%, 75% and 62% of neonates with sepsis respectively. Pathophysiologically non-oliguric renal failure appears to occur because of less severe reduction in GFR and apparent better preservation of tubular function. In a study by Pereira et al,[15] out of 20 cases of AKI (out of which 18 had sepsis), the incidence of oliguria was 80%.

In neonates, pre-renal failure is more frequent than intrinsic renal failure which is due to renal hypo-perfusion or ischemia. On the other hand, in the present study intrinsic renal failure was more predominant than prerenal failure. (85% versus 15%) similar to Mortazavi et al,[8] who reported that intrinsic kidney failure was more frequent than pre-renal failure in neonates (52% versus 42.4%). This is because of the fact sepsis can operate through a variety of mechanisms producing renal failure. It can cause renal failure by shock, DIC, haemorrhage, cardiac failure and through ATN.

In our study, it was found that most of the cases (53.84% of cases) of AKI in our study were found to be in Stage 1.

Majority of the babies with nonoliguric and oliguric AKI were detected in stage I. This study suggests that AKI can be detected at an early stage by measuring serial serum creatinine by using AKIN criteria. In our study, 69.24% babies with AKI survived and 30.76% of babies died. The relation between the mortality and AKI was statistically significant. This was comparable with the mortality rates in studies by Mathur et al[5] (70.2%) and S.K. Pradhan et al[14] (54.5%).

The mortality did not differ significantly (p>0.05) in oliguric AKI (33%) compared with non-oliguric AKI (30%) in the present study. This was in contrary with the studies by Mathur et al[5] and S. K. Pradhan et al[14] which showed the mortality was high in non-oliguric AKI than oliguric AKI.

Only one neonate with oliguric AKI required renal replacement therapy in the form of Peritoneal Dialysis and the baby died. All the neonates with AKI who survived had normal renal function at discharge with recovery time of two weeks.

CONCLUSIONS

AKI is a very common entity among septic neonates. The latent period for the development of AKI in neonatal sepsis is short. Coexisting shock and DIC were significantly associated with AKI and appear to be the main operating mechanisms causing AKI. The high mortality among septicaemic neonates with AKI stresses the need for septic neonates to be screened for renal failure, as early recognition of coexisting risk factors for AKI may reduce the risk of its occurrence and early intervention can lead to better outcome.

Limitations

Newborns who have had AKI are predisposed to the development of obesity, hypertension, and chronic renal failure in future. They need follow up with growth, nutrition, blood pressure, and the renal function status has to be monitored. Hence a study with a longer duration is needed to evaluate the measures necessary to reduce the incidence of morbidities.

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