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Original Research Article

Study of renal profile in septicemic neonates

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ABSTRACT

Background: Neonatal sepsis can cause multiorgan involvement causing neonatal morbidity and mortality. The kidneys are an important organ affected in septicemic newborns. In this study we evaluated the renal functions and its association with various risk factors along with outcome in septicemic neonates.
Methods: This study was a prospective observational study conducted in a tertiary care teaching hospital. The sample size was 276 cases of septicemic new-borns and study duration was 2 years. The profile of acute renal failure (ARF) and various risk factors were studied in a sample of 276 septicemic neonates. Detailed clinical examination and investigations were done to confirm the diagnosis of neonatal sepsis and the occurrence of ARF was studied among these septicemic newborns. Risk factors like birth weight, gestational age, shock, etiological agents, DIC were studied for the occurrence of ARF and mortality in ARF patients among septicemic neonates.
Results: 30.07% of septicemic neonates developed ARF. DIC (p value=0.014), shock (p value=<0.0001), gestational age (p value=0.005), birth weight (p value=0.003), were found to be analytically significant for the occurrence of ARF. Birth weight (p value=0.006), age of onset of sepsis (p value=0.019), shock (p value =<0.0001), oliguria (p value =<0.0001), and DIC (p value=0.015) were significant predictors of mortality in ARF among septicemic neonates.
Conclusions: Awareness and early identification of various risk factors and ARF in septicemic neonates can prevent morbidity and mortality among neonates.

Keywords: Neonate, Renal failure, Sepsis, Shock

INTRODUCTION

Neonatal sepsis is one of the most important causes of morbidity and mortality in newborn period. Sepsis is responsible for 30-50% of total neonatal deaths each year in developing countries.[1,2] The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births.[3] The causes of acute renal failure in neonates are multifactorial. Neonatal septicemia is associated with multiorgan dysfunction and is a leading cause for the occurrence of Acute renal failure (ARF). The most common form of ARF in neonates is prerenal failure, which is due to renal hypoperfusion.[4] Published studies estimate the incidence of ARF in critically ill neonates between 1% to 24 % and mortality rates between 10 to 16% in neonatal intensive care units.[4]

However, data on ARF in neonatal sepsis is scarce, and earlier studies have focused on perinatal asphyxia as the cause of ARF. Considering these facts, the present study was undertaken to study the renal profile in septicemic neonates and its association with other risk factors and etiological agents.

In this study our primary objective is to study profile of acute renal failure in neonatal sepsis. Secondary objective is to study the association of acute renal failure with risk factors and etiological agents in neonatal sepsis and to study the outcome of acute renal failure among septicemic neonates.

METHODS

This study was a prospective observational study conducted in the neonatal intensive care unit and neonatal sections of paediatric wards of a tertiary care teaching hospital. The study group consisted of 276 cases and study duration was 2 years. Neonates of both gender and all gestational age who were diagnosed as neonatal sepsis on the basis of either positive sepsis screen or culture positivity were included in this study. Neonates with congenital anomalies of kidney and urinary tract on clinical examination and ultrasound abdomen and those whose parents did not giving consent for enrollment in study were excluded. Cases were enrolled after obtaining written informed consent from parents. All selected cases had a full clinical evaluation including assessment of gestational age by modified Ballad's score, age at onset of sepsis, APGAR score at 1 min and 5min, birth weight by using electronic scale, maternal history, birth history. Venous samples were collected through a peripheral IV line and analyzed for:

- CBC, Hb, TLC, DLC, platelet count, hematocrit was done by automated coulter counter method.
- CRP done by latex slide test; CRP reagent kit based on principle of latex agglutination.
- Micro ESR by Wintrobe's tube method.
- Samples for blood culture was collected from a separate peripheral IV site. CSF and urine culture was also done.
- Blood culture was done by rapid automated microbial detection device, BacT/ALERT® 3D.
- Fungal culture was done in Sabaraud's agar.

All septicemic neonates underwent renal function test and samples were taken at 24, 72 hours and 7th day after diagnosis of neonatal sepsis which includes serum creatinine levels. SCr was tested by Jaffe's colorimetric method in an automated analyzer (principle: Jaffe's reaction). ARF in a septicemic neonate was diagnosed based on serum creatinine levels as given in Table 1 (5). 24-hour urine output was calculated using either by bag collection or urethral catheterization in VLBW babies. Coagulation profile was also done in all bleeding neonates.

Management of neonatal sepsis was done according to standard protocol of treatment. All septicemic neonates were followed after diagnosis of sepsis for the occurrence and outcome of acute renal failure and managed according to the protocol. Association with following risk factors was studied for the occurrence of ARF: gestational age, birth weight, age of onset of sepsis, culture positivity, birth asphyxia, DIC, shock. Association with following risk factors were studied for mortality in ARF: gestational age, birth weight, age of onset of sepsis, culture positivity, birth asphyxia, DIC, shock, oliguria.

Statistical analysis

Statistical analysis was done by using descriptive and inferential statistics using chi square test and z-test for difference between two means. Also, $p<0.05$ is considered as level of significance.

RESULTS

In this study, 124 septicemic neonates were male (44.92%) and 152 were female (55.07%). Among 276 septicemic neonates, 104 (37.68%) were preterm (<37 weeks) and 172 were (62.32%) term (≥37 weeks) neonates and 174 neonates (63.04%) were normal birth weight, 87 (31.52%) were low birth weight, 14 (5.07%) were very low birth weight and 1 neonate (0.36%) was extremely low birth weight.

Table 1: Normal serum creatinine values in term and preterm infants (mean, SD).

Age (days)	<28 weeks	28-32 weeks	32-37 weeks	>37 weeks
0-3	1.05, 0.27	0.88, 0.25	0.78, 0.22	0.75, 0.20
4-7	0.95, 0.36	0.94, 0.37	0.77, 0.48	0.56, 0.40
8-14	0.81, 0.26	0.78, 0.36	0.62, 0.40	0.43, 0.25
15-28	0.66, 0.28	0.59, 0.38	0.40, 0.28	0.34, 0.20

In this study, 30.07% of septicemic neonates developed ARF and out of that 29.9% and 44.4% of cases between 32-36 weeks gestation and <31 weeks gestation respectively.

Table 2: Number of cases and its distribution in the study.

Distribution of cases	No. of cases
Male	124 (44.92%)
Female	152 (55.07%)
Preterm (<37 weeks)	104 (37.68%)
Term (≥37 weeks)	172 (62.32%)
Sepsis screen positive	202 (73.18%)
Culture positive	74 (26.82%)
Early onset sepsis	159 (57.60%)
Late onset sepsis	117 (42.40%)
Normal birth weight	174 (63.04%)
Low birthweight	87 (31.52%)
Very low birth weight	14 (5.07%)
Extremely low birth weight	1 (0.36%)

Only 15.2% of term cases suffered ARF in neonatal sepsis. Among 74 culture positive septicemic neonates, almost 50% that is 37 neonates had *E. coli* grown in blood culture followed by CONS (16.21%), *Staphylococcus aureus* (6.75%), *Klebsiella* (5.40%), *Streptococcus pneumococci* (5.40%), *Enterobacter* (2.70%) and some other gram-negative organism were grown (13.51%). *E. coli* was significantly associated with ARF with a p value of 0.003. No previous studies have been found showing association of etiological agents with ARF in septicemic neonates. The ARF in this study was mainly non-oliguric (69.87%).

Table 3: Mean serum creatinine values in septicemic neonates.

Time of sample collection after diagnosis of sepsis.	With ARF (mg/dl)	Without ARF (mg/dl)
24 hrs	2.58 ±0.86	0.30± 0.08
72 hrs	3.02± 0.92	0.30±0.07
7th day	2.68±0.71	0.29±0.07

Comparison of neonates with and without ARF revealed many important details. Birth weight (p value = 0.003), gestational age (p value=0.005), shock (p value= <0.0001), DIC (p value=0.014), were significantly associated with ARF in septic neonates.

Table 4: Association of ARF among septicemic neonates.

Cases	With ARF	Without ARF	Total
Culture positive	25 (9.06%)	49 (17.75%)	74
Sepsis screen positive	58 (21.01%)	144 (52.17%)	202
Total	83 (30.07%)	193 (69.93%)	276

Other risk factors such as culture positivity (p value= 0.650), age of onset of sepsis (p value = 0.96), birth asphyxia (p value = 0.925), were not significantly associated with ARF in septic neonates. In our study, mortality in septic neonates with ARF was not significantly higher than non ARF patients (p value= 0.35).

Table 5: Association of oliguria in ARF among septicemic neonates.

ARF cases	Number	Percentage
Oliguric arf	25	30.12
Non-oliguric arf	58	69.88
Total	83	100

Various risk factors predicting the outcome in ARF in septicemic neonates were also studied. Prognostic factors studied in the present study are birth weight, gestational age, culture positivity, age of onset of sepsis, oliguria, shock, DIC, birth asphyxia. It was found that birth weight (p value =0.006), age of onset of sepsis (p value= 0.019), shock (p value =<0.0001), oliguria (p value = <0.0001), and DIC (p value = 0.015) were significant predictors of fatality in ARF among septicemic neonates. Other factors like culture positivity (p value = 0.58), birth asphyxia (p value = 0.30), and gestational age (p value=0.08) were not significantly associated with increased mortality in ARF among septicemic neonates.

Table 6: Outcome of ARF in septicemic neonates.

Outcome	With ARF	Without ARF	Total
Died	17 (6.16%)	25 (9.06%)	42
Survived	66 (23.91%)	168 (60.87%)	234
Total	83 (30.07%)	193 (69.93%)	276

DISCUSSION

Acute renal failure is quite common in neonatal sepsis. In neonate, kidney functions are not fully mature and functional maturation continues in postnatal period. Normally a neonate is able to cope with most of rapidly changing functional demands of body. However, in condition like sepsis, the adaptive capacities of kidney may be overcome leading to renal failure. Mechanisms of renal failure in sepsis are multiple. Sepsis is characterized by a generalized inflammatory response and activation of the coagulation and fibrinolytic cascades, resulting in endothelial injury. A broad array of humoral mediators is released in the systemic circulation, including cytokines, lipid mediators such as platelet activating factor and arachidonic acid metabolites, endothelin-1, and complement components. Systemic hypotension, resulting in renal ischemia, is a contributing, but certainly not the sole factor in septic ARF. Intrarenal vasoconstriction, owing to an imbalance between vasodilator and vasoconstrictor substances, results in a decline in renal blood flow (RBF) and abnormalities in intrarenal blood flow distribution that predominantly affect the outer medulla. Inflammatory cells infiltrate the kidney, causing local damage by release of oxygen radicals, proteases, and further production of inflammatory cytokines. Leukocyte-endothelial interactions result in physical congestion of the medullary vasculature and a further decreased regional blood flow. Dysfunction of the coagulation and fibrinolytic cascades contributes to intraglomerular thrombosis. Tubular injury leads to cell detachment with intratubular obstruction and tubular back leak. All these factors are responsible for development of septic ARF. Recovery from ARF requires clearance of necrotic tubular cells and debris, as well as regeneration and repair of the nonfatally injured cells.[3,4] Mathur NB et al showed that incidence of acute renal failure in septicemic neonates is 26%.[6] Griffin et al showed that 16% of septicemic neonates suffered from ARF.[7] Prevalence of ARF with neonatal sepsis in a study by Muhammad H et al was of 31.6% of studied cases.[8]

The exact incidence of neonatal ARF is difficult to quantify because neonates commonly have non oliguric

type of renal failure and therefore may not be screened with serum creatinine for ARF. The ARF in present study was mainly non-oligouric which contradicts the general perception that ARF in neonates is commonly oligouric. Griffin etal. showed all neonates who developed ARF in sepsis were oligouric.[7] But study done Mathur NB et al. showed that ARF in neonatal sepsis is predominantly non oligouric.[6] A high incidence of non-oligouric renal failure could be perhaps due to kidneys being studied in diuretic phase of ATN where oligouric phase being short and unnoticed.

It appears that shock and DIC are the two main mechanisms through which sepsis causes ARF in neonates. In the study by Mathur et al. Birth weight (p value = 0.008), DIC (p value = <0.001) and shock (p value = <0.001) was an important predictor of ARF in septic neonates.[6] The most common significant predisposing factors for ARF in a study by Muhammad et al were DIC (p value = <0.05) and shock (p value = <0.001).[8] In study done by Mathur et al had 2.5 times higher fatality among septicemic neonates with ARF.[6] Muhammad et al reported a neonatal mortality rate (NMR) of 72.2% in ARF associated sepsis cases.[8] This study is prospective observational type of study and the septicemic neonates who suffered from ARF were not followed on a long-term basis and residual kidney disease if develops in future could not be determined. All septicemic neonates were treated according to protocol with nephrotoxic drugs, so nephrotoxic drugs were not considered as separate risk factor for occurrence of ARF and fatality in ARF. The sample size is small, the validation of these results requires a large sample size.

CONCLUSION

Among 276 cases of neonatal sepsis in this study group 83 neonates (30.07%) have developed ARF. It was found that ARF in neonatal sepsis was predominantly non-oligouric. Risk factors like culture positivity, age of onset of sepsis, birth weight, gestational age, birth asphyxia, shock, DIC were assessed for the occurrence of ARF in neonatal sepsis. DIC, shock, gestational age, birth weight was found to be significantly associated with occurrence of ARF in univariate analysis.

In present study, fatality in septic neonates with ARF was not significantly higher than non ARF patients (p value=0.35). The fatality in ARF patients is 20.48% and in non ARF is 12.9%.

Various prognostic factors were also studied for their significance in predicting the mortality in cases of ARF. Birth weight, age of onset of sepsis, shock, oliguria, and DIC were significant predictors of fatality in ARF among septicemic neonates after doing univariate analysis. So, early identification and management of risk factors in septicemic neonates helps in preventing the occurrence and mortality in acute renal failure. Sr. Creatinine and urine output should be monitored in septic new-borns for early identification of acute kidney injury to prevent mortality and morbidity in new-borns.

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