Original Article

Acute Renal Failure in Neonatal Sepsis

N.B. Mathur, Himanshu S. Agarwal and Arti Maria

Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, India.

ABSTRACT

Objective. To evaluate the occurrence of acute renal failure (ARF) and the factors associated with it in cases of neonatal sepsis.

Methods. The case control study was conducted in the referral neonatal intensive care unit of a tertiary teaching hospital. 200 out born neonates with sepsis admitted to the nursery from January to July 2003 were evaluated for presence of ARF (cases) or not (controls). Sepsis was diagnosed on the basis of either a positive sepsis screen (immature: total (I:T) neutrophil ratio > 0.2, μ -ESR > age in days + 2 mm or >15 mm, CRP> 6mg/dl, TLC<5000 cells/mm^3; 2 or more positive) or a positive blood culture in symptomatic neonates. ARF was defined as blood urea nitrogen (BUN) >20mg/dl on two separate occasions at least 24 hours apart. Oliguria was defined as urine output <1ml/Kg/hr.

Results. 52 out of 200 (26%) neonates with sepsis had ARF; only 15% of ARF was oliguric. The mean gestation of neonates with ARF was similar to those without ARF (36.1±4.1 wks vs. 36.6±3.5 wk; p= 0.41). A significantly higher number of babies with ARF weighed less than 2500 gm as compared to those without ARF (86.5% *vs* 67.6%; p= 0.008). The association of meningitis, disseminated intravascular coagulation (DIC) and shock was also significantly higher in neonates with ARF (46.8% *vs* 26.2%, p=0.01; 65.4% *vs* 20.3%, p<0.001; 71.2% *vs* 27.0%, p<0.001 respectively). Mortality in neonates who developed ARF was significantly higher (70.2% *vs* 25%, p<0.001). Factors including gestational age, weight, onset of sepsis, culture positivity, associated meningitis, asphyxia, shock, prior administration of nephrotoxic drugs were subjected to univariate analysis for prediction of fatality in neonates with sepsis and ARF; only shock was found to be a significant predictor of fatality (p<0.001). ARF had recovered in 22 out of 49 neonates in whom data was available; three patients had left against medical advice. The mean duration of recovery in these 22 neonates was 5.5 days (range 1-14 days). Presence of co-existing morbidities (perinatal asphyxia/congestive heart failure (CHF)/ necrotising enterocolitis (NEC)) or nephrotoxic drugs did not alter the frequency of recovery of ARF in septic neonates (45.5% *vs* 44.4%,p=0.944; 41% *vs* 52%, p=0.308 respectively).

Conclusion. Renal failure occurred in 26% neonates with sepsis. Although ARF in neonates has been reported to be predominantly oliguric, it was observed that ARF secondary to neonatal sepsis was predominantly non oliguric. Low birth weight was an important risk factor for the development of ARF. The mortality being three times higher in neonates with ARF demands a greater awareness of this entity among practitioners and better management of this condition.
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Acute renal failure (ARF) is commonly present among sick neonates.[1,2] While asphyxia, Respiratory distress syndrome (RDS) and urogenital anomalies are commonly reported causes of ARF in the West, [3-5] sepsis is the leading cause of ARF in the preliminary reports from India.[6,7] However, data on ARF in neonatal sepsis is scarce, and earlier studies have focused on perinatal asphyxia as the cause of ARF. Criteria for ARF in neonates usually include a high Blood urea nitrogen (BUN) concentration (>20 mg / dl).[3,5,8-11] Renal failure in neonates has been reported to be predominantly oliguric. [7,10] However, occurrence of oliguria in ARF has not been evaluated in a cause specific manner. The present study was undertaken with the objective of evaluating occurrence of uremia and oliguria in neonatal sepsis, and the risk factors associated with it.

MATERIALS AND METHODS

The study was conducted in the referral nursery of Lok Nayak Hospital catering to out born neonates. Medical records of 200 cases of neonatal sepsis admitted from January to July 2003 were studied. Neonatal sepsis was diagnosed on the basis of either a positive sepsis screen or

Correspondence and Reprint requests : Dr. N B Mathur, Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi 110002, India. E- mail: drmathur @ nda.vsnl.net.in

a positive blood culture in symptomatic neonates. The screen was positive if 2 or more of the following were present – CRP > 6 mg/dl, micro- ESR > age in days+ 2mm or > 15mm fall in first hour, Total leucocyte count <5000/ mm^3, immature: total neutrophil ratio > 0.2.[7] Acute renal failure (ARF) was defined as blood urea nitrogen (BUN) >20mg/dl on 2 separate occasions at least 24 hours apart. BUN was done by the urease method. Oliguria was defined as urine output < 1ml/Kg/hr.[5,7,10,11] A thorough clinical examination to see for urethral, meatal abnormalities, palpable bladder and kidneys was done. None of the neonates included in the study had any gross congenital anomaly of the kidney or urinary tract on clinical examination. Out of the 27 patients in whom ARF did not recover, USG was done in 15 patients, and was found to be normal. In the rest USG could not be done because the neonates were too sick to be transported or had expired. In 22 patients who recovered from ARF, USG was done in 10 patients and was normal.

A retrospective case control study design was used. Risk factors evaluated for occurrence of ARF included gestational age, weight, age at onset of sepsis, culture positivity, meningitis, co morbid conditions (birth asphyxia, congestive heart failure (CHF), necrotising enterocolitis (NEC)), (disseminated intravascular coagulation) DIC and shock. In a sick child with clinical bleed, presence of low platelet count with a deranged prothrombin time was taken to be DIC.[12]

Risk factors evaluated for fatality in sepsis associated ARF included gestational age, weight, early onset, culture positivity, associated meningitis, asphyxia, shock, administration of nephrotoxic drugs and presence of oliguria. Statistical analysis was done by students t- test, Chi square test and Mann Whitney test.

RESULTS

Out of the 200 neonates with sepsis, 52 had uremia (26%). The mean gestational age of the study population was 36.5 weeks and 80 were preterms (40%). Mean weight at presentation was 2003 gms. Early onset sepsis constituted 53% of the cases, and meningitis was present in 31.8% of the total. 63.3% of the neonates survived. Renal failure was oliguric in only 15% of the cases. Renal failure had a mean onset at 1.38 days after the diagnosis of sepsis and 60% of the cases were diagnosed at presentation (Table 1).

Neonates with oliguric and non-oliguric renal failure were compared (Table 2). They did not differ significantly with respect to weight, gestation, onset and duration of ARF. Survival was lower in cases of oliguric ARF as compared to non-oliguric ARF (14.3% *vs* 32.5%) but was not statistically significant (p=0.4).

ARF recovered in 22 out of 49 neonates (44%), the mean duration of ARF in these was 5.5 days (range 1-14 days). Presence of coexisting morbidities (birth asphyxia, CHF, NEC) or nephrotoxic drugs (aminoglycosides, indomethacin) did not alter the frequency of recovery of ARF (Table 3).

TABLE 1. Clinical Profile of Study Population

Total number of neonates with sepsis	200
Mean gestational age (weeks ± s.d.)	36.5 ± 3.7
Preterm	40%
Mean weight at presentation (gms ± s.d.)	2003 ± 729
Mean age at presentation (days ± SEM)	7.14 ± 0.85
Early onset sepsis (≤ 72 hrs)	53%
Late onset sepsis (> 72 hrs)	47%
Culture positive sepsis	18.8%
Meningitis	31.8%
Survival	63.3%
ARF	52 (26%)
Oliguric	8 (15%)
Non oliguric	44 (85%)
ARF at presentation	31 (60%)

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

	Oliguric ARF	Non-oliguric ARF	p- value
No. of patients	8	44	
Mean gest. Age (wks ± s.d.)	37.5 ± 4.37	35.86 ± 2.5	0.078
Mean weight (gms± s.d.)	1976.87 ± 672.3	1769.5 ± 618.2	0.200
Early onset sepsis (%)	37	59	0.3
Culture positive sepsis (%)	0	15.9	0.3
Meningitis (%)	37.5	43.18	>0.5
Onset of ARF (days)	2.62	1.16	0.19
Duration of ARF (days)	4.95	4.85	0.47
Survival (%)	14.3	32.5	0.4
Nephrotoxic drugs (%)	50	47.7	>0.5
Shock (%)	87.5	68.18	0.3
DIC (%)	62.5	65.9	>0.5

Cases of neonatal sepsis with and without ARF were compared for various risk factors (Table 4). The difference between the two groups was significant with respect to frequency of low birth weight, associated meningitis, DIC and shock. The difference was not significant with respect to gestational age, onset of sepsis, co morbidities (birth asphyxia, NEC, CHF) or culture positivity. Mortality in neonates with ARF was very high (p<0.001)

A number of factors, which could predict ARF in septic neonates, were studied. Only shock and weight < 2500gms were sensitive predictors. Shock had sensitivity and specificity of 71% and 73% respectively while low birth weight had a good sensitivity (86.5%) with low specificity (32.4%). Asphyxia, gestational age and culture positivity were not good predictors of ARF in septic neonates (Table 5).

TABLE 3. Recovery of ARF

	Recovered N (%)	Not Recovered N (%)	p- value
ARF cases	22 (44%)	27 (56%)	
Co existing morbidities	10 (45.5%)	12 (44.4%)	0.944
Nephrotoxic drugs	9 (41.0%)	14 (52%)	0.308

TABLE 4. Comparison of Septic Neonates with and Without ARF

	With ARF	Without ARF	p -value
No. of Subjects	52	148	
Mean gest. Age (wks)	36.1± 4.1	36.6±3.5	0.41
Term ≥ 37 wk	61.5%	59.5 %	0.792
Preterm < 37 wk	38.5%	40.5 %	
Mean weight (gms)	1801.4±662.8	2074.2±740.8	0.20
Wt< 2500 g	86.5%	67.6%	0.008
Mean age at presentation (days)	6.03±0.95	7.84±0.66	0.9
Sepsis Early	55.8%	52.7%	0.703
Sepsis Late	44.2%	47.3%	
Culture positive sepsis	15.6%	20.0%	0.513
Meningitis	46.8%	26.2%	0.01
Co morbid conditions	44.2%	30.4%	0.07
DIC	65.4%	20.3%	< 0.001
Shock	71.2%	27%	< 0.001
Mortality	70.2%	25%	<0.001

TABLE 6. Prognostic Factors in Neonatal ARF

	Survived (n=14)	Died (n=33)	p -value
Gestational Age (wks)	37.86 ± 2.5	35.58 ± 4.49	0.127
Weight (gms)	2053 ± 592	1705.3 ± 611	0.099
Shock	28.6%	97.0%	< 0.001
Culture positive	21.4%	10.7%	0.350
Meningitis	46.2%	50.0%	0.817
Asphyxia	21.4%	30.3%	0.534
Early sepsis	42.9%	63.6%	0.188
Nephrotoxic drugs	28.6%	57.6%	0.069
Oliguria	7.1%	18.2%	0.314

TABLE 5. Antecedent Factors Predicting ARF in Septic Neonates

	ARF Present	ARF Absent	p-value	Sensit-ivity (%)	Specificity (%)	Positive predictive Value (%)	Negative predictive Value (%)
Wt < 2500g (%)	86.5	67.6	0.008	86.5	32.4	31.0	87.3
Gestational Age < 34 wks (%)	23.1	20.3	0.669	23.1	79.7	28.6	74.7
Shock (%)	71.2	27.0	<0.001	71.2	73.0	48.1	87.8
Asphyxia(%)	28.8	29.1	0.977	28.8	70.9	26.0	73.9
Culture Positive (%)	15.6	20.0	0.513	15.6	80.0	21.9	72.5

Various factors were studied for predicting fatality in cases of neonatal ARF. Only shock was a significant predictor of fatality, shock being present in 28.6% of those surviving and 97% of those who died. Factors like gestational age, weight, early onset sepsis, culture positivity, meningitis, asphyxia, nephrotoxic drugs, oliguria did not affect mortality (Table 6).

DISCUSSION

The neonatal kidney is particularly vulnerable to the effects of hypoperfusion since the renal vascular resistance and plasma renin activity are high. Consequently, renal blood flow is proportionately more reduced in neonates. Acute tubular necrosis (ATN) has many parallels with the physiologic characteristics of neonatal kidney- the low glomerular filtration rate (GFR), decreased intercortical perfusion, decreased proximal reabsorption of sodium and increased plasma renin activity. [13] The neonatal kidney has been described as 'halfway to acute renal failure'. [14]

Sepsis can operate through a variety of mechanisms in producing renal failure. It can cause renal failure by shock, DIC, hemorrhage, cardiac failure and through ATN. While sepsis has been said to be one of the important predisposing causes of ARF (90% cases),[7] the actual incidence of renal failure in all sepsis cases is not documented. In the present study, 26% of all neonates with sepsis had ARF.

ARF in neonates has been reported to be predominantly oliguric, incidence of oliguria varying from 46%-93%.[8] In the present study, incidence of oliguria in neonatal sepsis was only 15%. In studies evaluating ARF due to variable causes, perinatal asphyxia may be responsible for a higher frequency of oliguria. Prompt management of coexisting conditions such as shock may lead to less severe reduction in GFR and better preservation of tubular function and may account for lower incidence of oliguria in the present study.

ARF was present at the onset in 60% of the patients. Such a high percentage reinforces the fact that the neonatal kidney is very fragile and that the latent period for the onset of renal failure may be very short in neonates with sepsis. Another reason could be the delay in seeking medical attention for the neonates.

Comparison of neonates with and without ARF revealed many important details. Weight was an important predictor of ARF in septic neonates. Also, DIC and shock were two conditions which were much more common in patients with ARF. It appears that shock and DIC are the two main mechanisms through which sepsis causes ARF in neonates. Increased fibrin degradation products (FDP) are frequently found in the serum and urine of patients with ARF.[15] Temporary obstruction of peritubular or capillary vessels by fibrin deposits may therefore be an important factor in initiating the changes of tubular necrosis.[16] However, ARF was not found to be

more common in septic neonates with lower gestational age. Co morbid conditions such as birth asphyxia, CHF or NEC were not significantly associated with ARF in septic neonates.

The fatality among septic neonates with ARF was 2.5 times higher. This highlights ARF as an ominous complication in cases of neonatal sepsis, which has to be managed aggressively.

The present study has analyzed ARF in relation to neonatal sepsis. To the best of our knowledge, no such study focusing on ARF in neonatal sepsis has been published till date. The present study contradicts the general perception that ARF in neonates is commonly oliguric. Previous studies done by Jayashree *et al*[10] on birth asphyxia patients found 69.2% of ARF to be oliguric. In a study by Pereira *et al*[7] on 20 cases of ARF (out of which 18 had sepsis), the incidence of oliguria was 80%. The importance of DIC and shock as found in the present study has also been observed by other workers.[6,17] The mortality in neonatal ARF in the present study (70.2%), was not very different from those observed by other workers (50 to 78%). [5,11,18]

Various prognostic factors were also studied for their significance in predicting fatality in cases of neonatal ARF. Gestational age, weight, early onset sepsis, culture positivity, meningitis, asphyxia, oliguria, nephrotoxic drugs were not associated with increased mortality. Few authors, however, have found mortality in oliguric ARF to be significantly higher. [8,17]

CONCLUSION

The present study observations clearly reveal that ARF is a very common entity among septic neonates. Low birth weight is an important risk factor for the development of ARF in septic neonates. The latent period for the development of ARF in neonatal sepsis is short. Coexisting shock and DIC were significantly associated with ARF and appear to be the main operating mechanisms causing ARF. The high mortality among septic neonates with ARF stresses the need for septic neonates to be screened for renal failure.

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