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Study of Effect of Neonatal Septicemia on Renal Function

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Abstract: ***Aims & Objectives: To study the occurrence of ARF complicating neonatal sepsis and effect of associated contributing factors. Materials and methods: Over a period of 1 year from January to December 2013, out of 449 studied cases with neonatal sepsis, ARF complicated 104 (23.2%) of neonates. All cases were assessed in detail especially for co-morbidities: nephrotoxic drugs, DIC, shock, maternal drug intake and mechanical ventilation. A full sepsis screen and evaluation of renal functions by estimating the urine output and BUN was carried out for all studied babies. Sepsis was diagnosed on the basis of either a positive sepsis screen or a positive blood culture in symptomatic neonates. ARF was defined as blood urea nitrogen (BUN) >45mg/dl on two separate occasions at least 24 hours apart. Oliguria was defined as urine output <1ml/Kg/hr. Results: Oliguric ARF was found in 13.5% of cases. The mortality rate was 51.9% (54 cases) in ARF compared to 26.3% (91 cases) in sepsis without ARF. Low birth weight, DIC and shock were significant risk factors for ARF complicating neonatal sepsis (p<0.01,p<0.05,p<0.001). Recovery from ARF occurred in 50 (48%) cases. Conclusion: ARF complicating neonatal sepsis occurred in 23.2% of our study cases. It was significantly increased in the lower birth-weight and gestational age neonates, DIC and shock.***

Keywords: Septicemia, Neonate, ARF.

1. Introduction & Literature Survey

Sepsis remains a leading cause of morbidity and mortality among neonates in intensive care facilities[1]. Although the presence of multiple organ dysfunction and other co-morbidities certainly contributes to the high mortality[2]. Sepsis is characterized by a generalized inflammatory response and activation of the coagulation and fibrinolytic cascades, resulting in endothelial injury[3]. A broad array of humoral mediators are 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 results in renal ischemia, and contributes significantly to the development of septic ARF. Intra-renal vasoconstriction, owing to an imbalance between vasodilatory and vasoconstrictory substances, results in a decline in renal blood flow (RBF) and abnormalities in intra-renal blood flow distribution[4]. ARF occurs in as many as 3.4% to 24% of neonates admitted to neonatal intensive care units (NICUs)[5,6,7].The cause of ARF in neonates is multifactorial, and usually there is one or more associated contributing factor[8]. .ARF independently increases morbidity and mortality[6]. ARF is characterized by decreased GFR and renal tubular function compared to normal values for post-conceptional age.

Acute Renal Failure (ARF) is a complex disorder with clinical manifestations ranging from mild dysfunction to complete anuric renal failure. ARF may be oliguric or non-oliguric, depending upon the severity of the reduction in GFR and the degree of tubular reabsorption. Most often, ARF is recognized because of oliguria, although non-oliguric neonatal ARF is being detected with increasing frequency. Normal urine output is found in approximately one-third of neonates with ARF, although low urine output may occur in the absence of ARF. So, if urine output alone is used to assess renal function, ARF often will be either overlooked or over-diagnosed. The mortality of oliguric neonatal renal failure may be as high as 60% in medical ARF and even higher in neonates with congenital heart disease, or with anomalies of the genitourinary system. In contrast, non-oliguric renal failure in neonates has an excellent prognosis[7].

The incidence of intrinsic oliguric ARF in newborn infants admitted to the NICU ranges between 1-6% in retrospective studies and 6-8% in prospective studies[6].

2. Aims of the Study

In the following study, the aim was to evaluate the risk of occurrence of acute renal failure in cases of neonatal septicemia and to evaluate other contributing factors complicating ARF in these neonates.

3. Materials and Methods

This prospective case- control study was carried out on the high risk neonates who were admitted to the neonatal intensive care unit at B.J. Medical College and Civil Hospital, a central tertiary level care hospital in Ahmedabad, Gujarat. All babies admitted to the NICU in the period from January 2013 to December 2013, who were suspected of having neonatal sepsis, whether early-onset (EOS) or late-onset (LOS) were assessed for the presence of acute renal failure. Babies who had neonatal sepsis and complicated by ARF (Group I) are compared to those controls with neonatal sepsis without acute renal failure (Group II). All cases were studied prospectively and selected on the basis of presence of indices of neonatal sepsis using the department guidelines of sepsis screen. All selected cases had a full clinical evaluation including assessment of gestational age, birth weight, sex, Apgar Score at birth, maternal medications as anti-hypertensives, ACE inhibitors e.g. captopril, age of onset of sepsis, and the use of nephrotoxic drugs. Assessment of gestational age was done using the Ballard scoring system

for physical and neurological evaluation[11]. Birth weight was taken using an electronic scale measure for all studied cases on admission to the NICU. All sick and preterm babies (<37 weeks GA) are started on antibiotics, an aminoglycoside (amikacin) + β lactam(usually Ampicillin) from admission according to the guidelines of the department. Babies who received potentially nephrotoxic drugs such as indomethacin for patent ductus arteriosus (PDA) in preterm babies were also evaluated for renal functions.

Birth asphyxia was diagnosed if: Intrapartum fetal distress as assessed by the Apgar score <5 at 5 min of postnatal age, metabolic acidosis during 1st hour of age.

Venous samples were collected through a peripheral IV line and analyzed for a complete blood count (CBC), CRP, ESR and serum glucose; blood culture was collected from a separate peripheral IV site.

Urine quantification was done either by bag collection, or urethral catheterization in VLBW babies in which urine bag collection is difficult due to small amount of urine in these babies. Catheterization is used if an infant has failed to pass urine by 36-48 hours of age and is not hypovolemic.

The CBC samples were collected in EDTA and the differential count is done with Leishman stain to calculate the immature to total (I:T) ratio. Venous blood samples for CRP were analyzed using semi-quantitative reagent kit. It was considered significant if >0.6mg/dl. Venous blood samples for ESR estimation were collected on Na citrate and analyzed using the Westergren ESR pipette. For blood culture, 1-2ml of venous blood was withdrawn using a complete aseptic technique, into a blood culture bottle (10 ml) & was incubated at 37ºC for 7 days and were examined daily for growth. Any sign of growth was followed by subculture and identified by gram stain and biochemical reaction. BUN was done using Modified Urease method.

Sepsis was diagnosed on the basis of positive sepsis screen. A sepsis screen was considered positive if two or more of the following were present- immature: total (I:T) neutrophil ratio > 0.2, micro ESR > age in days + 2 mm or >15 mm, CRP> 0.6mg/dl, TLC<5000 cells/mm3; 2 or more positive or a positive blood culture.

If neonatal sepsis was suspected, collection of 24 hours urine was requested, and the amount of urine collected was recorded every eight hours, and adjusted to the daily fluid intake. BUN was collected 24 hours after the clinical diagnosis of sepsis and repeated 48 hours later or as needed.

ARF was diagnosed on the basis of blood urea nitrogen (BUN) >45mg/dl on two separate occasions at least 24 hours apart & Oliguria was diagnosed when urine output was <1ml/Kg/hr. Babies were assured to be well hydrated and receiving adequate amount of fluids.

Exclusion criteria:
Babies with major congenital malformations or presence of urogenital malformation were excluded.

Ethical aspects:
A written consent was taken from the parents of babies included in the study. The clinical condition of each studied case was explained to the parent before the consent was signed as well as the procedures done for each individual case. The parents were informed that the management of their neonate is running according to the guidelines of management of such cases in the department. Babies of parents who refused to sign were excluded from the study.

4. Results

Four hundred and forty nine babies with neonatal sepsis were included in the study, 104 cases with ARF (23.2%) in Group (I) and 345 cases without ARF acting as controls (76.8%) Group(II).

Table: I shows the clinical profile of both studied groups. The mean (SD) gestational age was 34.1 ± 4.4 in group (I) compared to 37.1 ± 3.7 in group (II). The mean birth weight was significantly lower in cases with ARF compared to cases of neonatal sepsis without ARF (2100 ± 470 vs 2550 ± 530 grams respectively).

The overall male to female ratio in the study group was 1.6:1 in group (I) compared to 1.38:1 in group (II).A significantly higher number of babies with ARF weighed less than 2500 gm as compared to those without ARF (87.5% Vs 65.2%, $p<0.01$).

Sepsis was confirmed by positive blood culture reports in 296 cases (65.9%), 183 cases being early onset (61.8%) and 113 cases being late onset (38.2%).

Acute Renal Failure was diagnosed in 23.2% (104 cases) of neonates with sepsis, 64 (61.5%) males and 40 (38.5%) females. Oliguric ARF was found in 13.5% (14 cases) in our study group. The mean duration of recovery from ARF was 5.5 days. Recovery from ARF occurred in 48.1% (n=50) of cases. The mortality rate was 51.9% (54 cases) in ARF compared to 26.4% (91 cases) in sepsis without ARF.

Fifty seven cases (54.8%) of ARF had EOS, and 45.2% of cases had LOS, compared to 39.1% & 60.9% of cases respectively in non-renal failure cases Table: II.

Disseminated Intravascular Coagulation (DIC) occurred in a significantly higher frequency in cases with ARF (64.4% Vs 29.3%, $p<0.05$). Similarly, shock complicating sepsis – ARF was significantly higher than in non ARF sepsis cases (72.1% versus 28.1%, $p<0.001$). On the other hand, nephrotoxic drugs, as a compounding factor, had no statistically significant effect upon the occurrence of ARF among the two groups, and accounted for 48.1% in ARF group versus 51.9% in sepsis without ARF, while perinatal asphyxia was present in 32.7% & 34.5% of cases of sepsis with and without ARF respectively. More cases with ARF were mechanically ventilated (44.3% vs 31.6%) although the difference was not statistically significant among both groups. The maternal drug intake in the peri-partum period had no significant effect on the occurrence of ARF (51.9% Vs 36.2%). Most neonates had more than one predisposing factor. Among admitted neonates with ARF, mortality rate was significantly higher than among cases without ARF (51.9% & 26.3% respectively).

5. Discussion

Acute renal failure (ARF) is a common complication of neonatal sepsis and carries an ominous prognosis. Prevalence of ARF with neonatal sepsis in our study accounted for 23.2% of studied cases. Although ARF in neonates has been reported to be predominantly oliguric, it was observed that ARF secondary to neonatal sepsis was predominantly non-oliguric. Fortunately, the prognosis for non-oliguric ARF is excellent unless multiorgan failure results. In our study, ARF was predominantly non-oliguric, while oliguric ARF accounted for 13.5% of cases with neonatal sepsis. Predisposing factors such as perinatal asphyxia, DIC and shock compromises the renal blood flow and hence the reduction in glomerular filtration rate (GFR) with resulting oliguria. Anticipation of such conditions and appropriate corrective measures should be implemented to improve renal perfusion and GFR.

The prevalence of ARF in boys is more than girls (male to female ratio 1.6:1), which is in agreement with reports from other studies[7,11,12].

Mortality rate of 51.9% was found in ARF associated sepsis cases, which was significantly higher than in sepsis without ARF (26.4%). Recovery occurred in 48.1% of ARF cases and the recovery rate was higher in the more advanced gestational age groups.

The most common significant predisposing factors for ARF in our study were DIC and shock. Cases who suffered DIC and shock were associated with significantly increased mortality ($p<0.05$).
Perinatal asphyxia, mechanical ventilation, nephrotoxic medications, maternal medications did not alter the frequency of ARF in septic neonates.

Preterm neonates were more vulnerable to develop any or several of these clinical conditions. Nephrotoxic drugs induced ARF, displayed by Aminoglycoside nephrotoxicity typically presents with non-oliguric ARF, with urinalysis showing minimal urinary abnormalities. The incidence of aminoglycoside antibiotic nephrotoxicity is related to the dose and duration of the antibiotic therapy as well as the level of renal function prior to the initiation of aminoglycoside therapy. The etiology is thought to be related to the lysosomal dysfunction of proximal tubules and is reversible once the aminoglycoside antibiotics have been discontinued. However, after discontinuation of aminoglycoside, the serum creatinine may continue to increase for several days due to ongoing tubular injury from continued high parenchymal levels of the aminoglycoside[10]. Mothers of infants with acute renal failure received more drugs during pregnancy and delivery (mainly anti-hypertensive and NSAIDs). NSAIDs interference with endogenous renal prostaglandin production will increase angiotensin II- dependent vasoconstriction, leading to reduced GFR and renal insufficiency. It is therefore important to monitor closely renal function in pre-term infants receiving indomethacin. ACE inhibitors taken by pregnant mothers cause profound hypotension, anuria, and may even precipitate ARF in neonates.

In some studies, the mortality rate in oliguric ARF due to acquired conditions such as asphyxia and sepsis was 60%[2,9] in our study the mortality was 51.9%.

In a study by Mathur and co-workers in India, 26% of septic neonates developed ARF[8]. Mortality of ARF among neonates with septicemia is high, 70.2% Vs 25% in neonatal septicemia without renal failure. Similarly, like other studies, mortality of ARF in septic neonates was significantly higher than non septic patients in our study. Agras et al.[12] found a 25% hospital mortality rate in neonates with ARF. Premature infants constituted 31 % of their cases, and many (47%) of their patients had non-oliguric renal failure. Mathur et al[8] prospectively studied mostly term neonates with sepsis and found a 26% incidence rate of ARF. The mortality rate was significantly higher in those with ARF than in those with no ARF (70.2% Vs 25%, p <0.001).

Delayed presentation and recognition of neonatal sepsis is associated with rapid development of multi-organ dysfunction and increased risk of mortality. The mortality being several times higher in neonates with ARF demands a greater awareness of this entity.
The commonest significant predisposing factors for ARF in our patients with sepsis were shock and DIC. Perinatal asphyxia, mechanical ventilation and nephrotoxic drugs played important roles but did not significantly affect the occurrence of ARF. Acute renal failure occurred more frequently in low birth weight neonates with sepsis although the difference was not significant.

6. Conclusion

Acute renal failure complicating neonatal sepsis is predominantly non- oliguric. Early recognition of predisposing risk factors for ARF and rapid effective correction of contributing conditions such as improper oxygenation, adequate ventilation and cardiac output, blood pressure abnormalities, and early treatment of sepsis is needed for prevention and effective management of ARF. The early detection of oliguria and monitoring of renal functions are imperative to reduce mortality and morbidity in neonatal ARF.

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Table 1: Clinical profile of babies with Neonatal Septicemia

	Group I *n = 104 (23.2%) (ARF Group)*	*Group II* *n = 345 (78.6%) (Non ARF Group)*	*P value*
Gestational age (weeks) Mean SD	34.1 ± 4.4	37.1 ± 3.7	NS
Birth weight (grams) Mean SD	2100 ± 470	2550 ± 530	< 0.05
LBW (<2500 grams) n(%)	91 (87.5%)	225 (65.2%)	<0.01
Sex (male/female ratio)	1.6:1	1.38:1	NS

NS- Not Significant

Table 2: Correlation of associated morbidities with ARF

	Group I n (%)	Group II n (%)	P value
EOS (<72 hrs)	57 (54.8%)	135 (39.1%)	NS
LOS (>72 hrs)	47 (45.2%)	210 (60.9%)	NS
Nephrotoxic drugs	50 (48.1%)	179 (51.9%)	NS
Perinatal asphyxia	34 (32.7%)	119 (34.5%)	NS
DIC	67 (64.4%)	101 (29.3%)	<0.05
Shock	75 (72.1%)	97 (28.1%)	<0.001
Mechanical ventilation	46 (44.2%)	109 (31.6%)	NS
Maternal drug intake	54 (51.9%)	125 (36.2%)	NS
Mortality	54 (51.9%)	91 (26.4%)	<0.001

NS: Not significant