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Undiagnosed renal failure in non-oliguric sick newborns

Anil Lahoti, Gajanand Singh Tanwar*

Department of Pediatrics, S. P. Medical College, Bikaner, Rajasthan, India.
Correspondence Address: * Gajanand Singh Tanwar, A-12, PBM Campus, Bikaner, Rajasthan, India.

Abstract
Critically ill newborns are at greater risk of developing ARF. Non-oliguric renal failure is becoming increasingly recognized in newborns. Acute renal failure is best prevented; hitherto, early recognition and appropriate treatment could be life saving in some instances. The present study was carried out to determine the incidence, clinical features, etiology and outcome of oliguric and non-oliguric renal failure in sick newborns admitted in neonatal unit, pediatric hospital, Bikaner. Consecutive 100 hospital born & 100 out born sick newborns admitted in pediatric neonatal unit, S. P. Medical College, Bikaner were studied. Incidence of ARF was 17.5% in hospitalized sick newborns. Incidence of functional Renal Failure was 37.14%, while 62.86% cases were of Intrinsic Renal Failure. Incidence of non-oliguric renal failure (54.55%) was more than oliguric renal failure (45.45%). Mean urine output in oliguric newborn was 0.60±014 ml/kg/hr while in non oliguric was 1.92±0.63 ml/kg/hr ($p<0.01$). Non oliguric ARF cases had lower mean serum urea level (103.77 ±58.25) as compared to oliguric ARF (146.95±83.23)($p<0.01$). Other renal indices were comparable in both oliguric non oliguric groups. The case fatality ratio was similar in non oliguric ARF (25%) as compared to oliguric (50%). Mortality was higher in preterm, LBW babies, advanced age at the time of diagnosis, outborn and intrinsic renal failure cases. Neonatal septicemia was leading cause of mortality (47.62%) followed by NEC, shock, RDS/pneumonia and perinatal asphyxia. An obvious implication of our study is that the habit of monitoring only urine volume as an index of renal function may be seriously misleading.

Keywords: Renal Failure, Oliguric ARF, Non-Oliguric ARF, Sick Newborn

Introduction

Kidneys are the essential organs of the human body. The milieu interior of the body is maintained in a balanced state by kidneys. Apart from fetal life, where placenta takes part in excretion of metabolic wastes, normal renal function is essential for life. A rapid deterioration of glomerular filtration rate leading to retention of nitrogenous waste products is known as acute renal failure. During the period of acute renal failure, excretory function of kidneys is deranged leading to accumulation of toxic substances in blood, volume expansion and electrolyte disturbances. This biochemical disequilibrium contributes to the morbidity and mortality. This condition should be timely diagnosed, as temporary replacement therapy in the form of dialysis can improve survival. Acute renal failure in the newborn

is increasingly attracting the attention of pediatrics nephrologists the world over. In a full term newborn, the kidney functions are not fully mature and functional maturation continues in postnatal age. Under normal circumstances the kidneys adapt to various endogenous and exogenous stresses. However, in critically ill newborns and stressful conditions like septicemia, the adaptive capacities of the kidney may be overcome leading to renal dysfunction. Rapid advances in technology and a better understanding of neonatal physiology have resulted in a vast improvement in the quality of care of critically ill newborns.

The etiology of renal failure in newborns in the tropical countries is distinctly different from that observed in the western countries, as is the availability of diagnostic and therapeutic facilities. Hence it was planned to determine the epidemiology, etiology, clinlical features and clinical course of oliguric and non-oliguric renal failure in hospitalized sick newborns admitted in pediatric neonatal unit, Bikaner.

Materials and methods

Present prospective study was conducted at department of pediatric medicine, Sardar Patel Medical College, Bikaner. Among the sick newborns (age less than or equal to 28 days) admitted in pediatric neonatal unit during this period, condecutive100 hospital born and 100 outborn newborns were selected for the study. Thirty five newborns had acute renal failure or developed acute renal failure during this study period. These babies constitute the material for this study.

A detailed history was taken in all cases. All the complaints such as decreased urine output, seizure, vomiting, sluggishness etc. were noted in preset proforma. A detailed examination of cases was done. Gestational age was assessed by modified Ballard's score. Attention was given to factors such as shock, features of septicemia, respiratory distress and any external malformations. Histories of any preexisting maternal illnesses or illness complicating the course of pregnancy such as fever, rash etc. were noted. Any history of oligohydramnios was specifically asked. Wherever available, antenatal sonogrpahy findings were recorded. The duration of pregnancy till delivery, nature and place of delivery and any factor complicating delivery and newborn resuscitation was noted.

Initial emergency measures such as suction, oxygen, ventilation and fluid resuscitation was provided to the cases as needed. Blood urea and creatinine was measured in all cases before initiation of treatment. Simultaneously urine output was noted. If patient was already dehydrated at the time of admission, his hydration was corrected. Patients without oliguria and normal urea and creatinine levels were excluded from the study. Babies with oliguria and without features of hypervolemia were given a normal saline bolus in a dose of 20 ml/kg over a period of one hour. A further change in urine output was noted. If oliguria persists in spite of fluid resuscitation or if patient is hypervolemic at time of admission or have CHF, and there is no contraindication to diuretics, then furosemide challenge in a dose of 1 mg/kg was given and changes in urine output was noted. Urine collection of approximately 12 hours was made by spontaneous micturation into clean urine collection bag. Simultaneous blood urea and serum creatinine was estimated.

If urine output increases to more than 1 mg/kg/hr within 24 hrs and there is no biochemical evidence of persisting renal dysfunction after 72 hours, the oliguria was labeled as prerenal and the case was enrolled in the study as functional renal failure. If urine output does not increase to >1 ml/kg/hr within 24 hrs or if biochemical evidence of persisting renal dysfunction was noted, then the cases was diagnosed as having intrinsic oliguric renal failure and enrolled into the study. If urine output increases and biochemical recovery was

noted but renal sonography shows altered echo texture suggestive of medical renal disease, then the case was enrolled in the study as intrinsic oliguric renal failure. If the patient had persistently deranged renal function in the absence of oliguria i.e. urine output more than 1ml/kghr, then patient was diagnosed as having non-oliguric renal failure and was enrolled in the study.

Any newborns having renal dysfunction due to obstructive uropathy or expired before documentation of persisting renal dysfunction were excluded fron the study.

Those cases excluded from the study at the time of admission were managed as needed. However if any of these babies developed oliguria or renal dysfunction was suspected during hospital stay, these cases were reevaluated for renal failure. If finding to have intrinsic renal failure then these cases were included in the study.

All related investigations were done in all cases enrolled in the study like Complete blood count, septic screen, renal function test, serum electrolyte, blood culture, renal sonogrpahy, complete urine microscopic and biochemical examination. Renal indices studied were Urinary sodium, Urine/Serum sodium, Urine/serum creatinine, Fractional excretion of sodium (FENa) [(Urine/serum sodium ÷ Urine/serum creatinine) x 100], Renal Failure Index (RFI) (Urine sodium ÷ Urine/serum creatinine). Serum creatinine was measured by modified method of Jaffe. Serum urea estimation was done by modified method of diacetylmonooxime kit. Serum sodium and potassium were done by semi auto analyzer. Urine sodium and potassium were done by Biomed digital flame photometry. Other investigations as per need of the case were also done. Continuous monitoring of case using hospital stay was done & course of illness was noted.

Results

Consecutive 100 hospital born and 100 outborn sick newborns admitted in pediatric neonatal unit, S. P. Medical College, Bikaner were selected for the study. Acute renal failure (ARF) was detected in 35 (17.5%) sick newborn in which 17 were hospital born and 18 were outborn. Further division in type of acute renal failure was functional renal failure in 13 newborn (37.14%) and intrinsic renal failure in 22 newborn (62.86%). Non-oliguric renal failure occurs more often then has previously been recognized. In the present study, 12 (54.55%) had nonoliguric renal failure while 10 (45.45%) had oliguric renal failure. (Table 1).

The male:female ratio was 1.92:1in ARF. In intrinsic ARF, mean weight and mean gestational age in oliguric and non oliguric ARF were 2.31 kg & 2.71 kg and 36.2 weeks & 36.8 weeks respectively. Non oliguric ARF tends to occur in higher weight group. Hospital born cases diagnosed earlier than out born cases. All cases diagnosed after 7 days of age were outborn. Most of the newborns presented with multiple symptoms. Sluggishness and refusal for feed were most common symptoms at presentation. Birth asphyxia was the most common cause of ARF in cases diagnosed before 3 days of age. Septicemia was leading cause in cases diagnosed after 3 day of age.

Table 1: Incidence of ARF in sick newborns.

	Newborn	ARF	Functional ARF	Intrinsic ARF		
				Total	Oliguric	Non-oliguric
Hospital Born	100	17	7	10	5	5
Outborn	100	18	6	12	5	7
Total	200	35 (17.5%)	13 (37.14%)	22 (62.86%)	10 (45.45%)	12 (54.55%)

Table 2: Comparison of biochemical parameter in sick newborn with oliguric and non-oliguric ARF.

Biochemical Parameter	Oliguric ARF (Mean± SD)	Non-oliguric ARF (Mean± SD)	p- value
Serum Urea (mg\dl)	146.95 ± 83.23	103.77 ± 58.25	0.01
Serum Creatinine (mg\dl)	2.61 ±1.28	2.11 ± O.23	0.52
Urine Sodium **(**meq\l)	88.54± 10.05	79.06 ± 15.97	0.03
Urine\ Serum Creatinine	10.82 ± 2.31	9.99± 4.02	0.52
Urine output (ml\kg\hr)	0.60 ± 0.14	1.92 ± 0.63	0.01
FENa	6.44 ± 1.80	6.31 ± 2.46	0.56
RFI	8.66 ± 2.59	8.84 ± 3.32	0.72 NS

Mean urine output in oliguric was 0.60±014 ml/kg/hr while in non oliguric was 1.92±0.63 ml/kg/hr [p<0.01]. Non oliguric ARF cases had lower mean serum urea level (103.77 ±58.25) as compared to oliguric ARF (146.95±83.23) (p<0.01). Other renal indices were comparable in both oliguric non oliguric groups. (Table 2).

The most common disease associated with ARF was neonatal septicemia (60%) followed by respiratory distress syndrome or pneumonia (31.42%), perinatal asphyxia (28.57%) & shock (28.57%). In outborn newborns neonatal septicemia and shock are more commonly associated while perinatal asphyxia is more commonly associated in hospital born newborn (p< 0.01).

The prognosis of nonoliguric ARF is better than that of oliguric ARF. The case fatality ratio was less severe in non oliguric ARF (25%) as compared to oliguric (50%). However, nonoliguric ARF is still associated with a substantial morbidity that only 2 (16.66%) newborn had normal renal function within 7 days in non oliguric type while in oliguric ARF cases, 4 (40%) newborn recovered successfully within 7 days. (Table 3).

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 newborns.

Table 3: Duration of normalization of biochemical abnormalities in oliguric and non-oliguric ARF.

Duration (in days)	Oliguric ARF (N =10)	Non-oliguric ARF (N =12)
3-4	1 (10 %)	0
5-7	3 (30 %)	2 (16.66 %)
8-14	0	6 (50 %)
>14	1 (10 %)	1 (8.33 %)
Died before normalization	5(50 %)	3 (25 %)
χ^2 =7.58	p =0.05	

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. The neonatal kidney has been described as 'halfway to acute renal failure' (Gupta et al. 2005 and Mathur et al. 2006).

Among the sick newborns admitted in pediatric neonatal unit, S.P.Medical college, Bikaner, 100 hospital born & 100 out born were evaluated and 35 (17.5%) had ARF out of which 17 (17%) in hospital born & 18 (18%) in out born newborns which is comparable. Incidence of functional renal failure was 37.14%, while intrinsic renal

failure was found in 62.86% newborn which include both oliguric (45.45%) & nonoliguric (54.55%) type of ARF. In the series reported by Ellis NE et al. 1982, 38% (17 out of 45 cases) had prerenal ARF, 40% (20 out of 45 cases) had intrinsic ARF and 18% (8 out of 45) had other causes. These value correlates well with incidence of ARF in our study.

Newborns with oliguric and non-oliguric renal failure were compared. They did not differ significantly with respect to weight, gestation and duration of onset of ARF. The mean gestational age in case of ARF was 35.94 weeks. It was 36.11 weeks in hospital born & 35.77 weeks in outborn cases. The mean gestational age of oliguric ARF (36.2 weeks) correlate well with the findings of other workers (Ellis NE et al. 1982 and Norman ME et al. 1979). However, mean gestational age of non oliguric ARF cases (36.8 weeks) was slightly higher form reported value of other workers (Lawrance, G et al. 1982). In intrinsic renal failure; preterm have more (50%) oliguric failure then term babies (40%). With maturation of renal function incidence of non oliguric ARF increases.

In this present study, ARF was seen more frequently (62.85%) in lower weight group (<2.5 kg). The less mature renal function and increased severity of precipitating illness in lower weight preterm newborns may be responsible for this finding. Mean weight in oliguric ARF was 2.31 kg & in non oliguric ARF was 2.71 kg. Oliguric ARF was seen more frequently in lower weight group (53.84%) as compare to (33.33%) in normal weight newborns.

In the present study, neonatal septicemia was the most common morbidity (60%) associated with ARF and in 38.57% of sick newborn, shock is the proceeding event due to dehydration, sepsis/asphyxia. Thus, indicating significant association between septicemic shock & ARF. This suggest that an initial episodes of shock due to sepsis causes renal asphyxia & ischemia which triggers renal failure (Jayashree, G et al. 1991). Septicemia contributes to ARF in 40-93 per cent of cases in both developed and third world countries (Lawrance, G et al. 1982, Nammalwar, B.R. et al 1987 and Pereira, B.J et al. 1989).

It was further noted that all the biochemical parameters were significantly lower in non oliguric group, but both FENa and RFI were >3 in this group also. The mean urea and creatinine in oliguric ARF (146.95±83.23 and 2.61±1.28) was higher than the value in non oliguric ARF group (103.77±58.25). This is probably due to better recovery of renal function in non oliguric ARF. Few cases of oliguric ARF fail to recover early leading to very high individual value (upto 255mg/dl urea and 5.2mg/dl of creatinine). This also led to higher mean value in this group. The mean urea creatinine observed by other workers had a wide range. Ellis NE et al noted mean urea of 99mg/dl and mean creatinine of 2.5mg/dl (Ellis NE et al. 1982). Jayshree et al. (1991) reported mean blood urea value of 94.15 mg/dl in cases of ARF due to perinatal asphyxia.

The mean urine output in oliguric ARF was 0.60±0.14 ml/kg/hr. It was 1.92±0.63 ml/kg/hr in non oliguric ARF. Normal ME and Asadi FK reported the mean urine output in oliguric ARF to be 0.25ml/kg/hr (Norman et al. 1979). Lawrance, G. et al. (1982) reported the mean urine output in non oliguric ARF to be 2.45 ml /kg/hr. Pereira B et al. (1989) reported oliguric ARF with urine output of 0.37 +/- 0.16 ml/kg/h while the nonoliguric ARF with urine output of 2.4 +/- 0.7 ml/kg/h. The difference in patient characteristics with respect to weight gestational age and precipitating illness may be responsible for this difference. In non-oliguric ARF, 83.33% newborn had not normalized renal function before first week while in oliguric ARF 40% resolved within 7 days. This may be due to better response of oliguric ARF to fluid therapy then non-oliguric.

Outcome

The prognosis and outcome of ARF patients depend on the early diagnosis of the conditions, the underline pathology, associated risk factors and the type of renal failure whether oliguric or non oliguric, functional or intrinsic.

Out of 35 newborns had ARF, 24 (68.57%) were cured and discharged. Eleven newborn (31.43%) died in which mortality in functional ARF was 3 (8.57%) and in intrinsic ARF was 8 (22.86%). The case fatality rate was less severe in non oliguric ARF (25%) as compared to oliguric (50%). Agras PI et al. (2004) reported the mortality rate in the 45 ARF cases was 24.4%, while Griffin et al. (1976) reported 25% mortality in ARF patient. Functional renal failure and intrinsic renal failure had significant different values of all renal function. In functional renal failure all the deranged renal functions were came to normal early, while in intrinsic renal failure cases no significant improvement, rather renal functions shows increase derangement.

Better the survival with increasing gestational age. Mortality is 66% in gestational age <32 weeks, 36.36% in gestational age 32-36 weeks and 20% in term newborns with ARF. Higher mortality in preterm may be due to associated disease with ARF have higher co-morbidity in this vulnerable group. In our study low birth weight with ARF had poor prognosis. VLBW babies had mortality of 71.42% while normal weight babies it was 15.38%. Mathur NB et al only shock and weight < 2500gms were sensitive predictors of outcome in ARF of newborns. 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%) (Gupta et al. 2005 and Mathur et al. 2006).

In the newborn, the prognosis and recovery from acute renal failure is highly dependent upon the underlying etiology of the acute renal failure. Factors that are associated with mortality include multiorgan failure, hypotension, need for pressors, hemodynamic instability, and need for mechanical ventilation and dialysis. The mortality and morbidity of newborns with acute renal failure is much worse in newborns with multiorgan failure. Newborns who have suffered substantial loss of nephrons as may occur in cortical necrosis are at risk for late development of renal failure after apparent recovery from the initial insult. Similarly, hypoxic/ischemic and nephrotoxic injury to the developing kidney can result is decreased nephron number. Newborns with acute renal failure need life-long monitoring of their renal function, blood pressure, and urinalysis.

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