Renal Failure in Asphyxiated Neonates

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A prospective case controlled study was conducted in the NICU of a tertiary level referral teaching hospital to determine the incidence of renal failure in asphyxiated neonates and to correlate severity and type of renal failure with Apgar score and hypoxic ischemic encephalopathy (HIE) grading of the neonates. Ninety-eight neonates were enrolled–70 asphyxiated babies and 28 healthy controls. Renal functions were assessed using urinary output, urine microscopy, biochemical parameters and sonographic findings. Babies having renal failure were managed on a protocolised plan and followed up till 6 months of age to detect any residual impairment.

Blood urea and serum creatinine were significantly higher in asphyxiated babies compared to the control group (P<0.001). Biochemical derangements correlated well with HIE staging and Apgar scores. There was no significant difference in urine output in the control and the study group as significant oliguria was seen in only 7 of the 70 asphyxiated babies and the output did not correlate with severity of asphyxia. Serum sodium level and fractional excretion of sodium showed significantly different values in the asphyxiated babies compared to control. Of the 70 asphyxiated -babies 33 (47.1%) had renal failure, which was of the non-oliguric type in (26/33) 78% cases and oliguric type in (7/33) 22% cases. Sonographic abnormalities were seen more often in oliguric babies and was associated with a bad prognosis. Renal parameters normalized in all neonates by 6 months of age. Mortality was higher in babies with oliguric renal failure. We conclude that renal failure is a significant problem in asphyxiated neonates with majority of babies having non-oliguric failure. Severity of renal function abnormality correlates well with degree of asphyxia. Oliguria, hyponatremia and abnormal sonographic scan are bad prognostic signs in renal failure secondary to birth asphyxia.

Key words: *Birth asphyxia, Hypoxic ischemic encephalopathy, Renal failure.*

BIRTH asphyxia is an eventuality having far reaching consequences in the neonatal period. Overall incidence of asphyxia is reported to vary from 1 to 1.5% at various centers(1) and is related to birth weight and gestational age of the baby. Hypoxia and ischaemia can cause damage to almost every tissue and organ of the body and various target organs involved have been reported to be kidneys in 50% followed by CNS in 28%, CVS in 25% and lungs in 23% cases(2).

As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxic ischaemic episode, which if prolonged, may even lead to irreversible cortical necrosis. Early recognition of renal failure is important in babies with HIE to facilitate appropriate fluid and electrolyte management as a stable biochemical milieu is vital. Diagnosis of renal failure is difficult in neonates as many of the established clinical and biochemical

parameters are unreliable in this age group. We performed this study to determine the incidence of renal failure in birth asphyxia and to correlate the severity and type of renal failure with Apgar score and HIE grading of asphyxiated neonates.

Subjects and Methods

This study was undertaken in the NICU of a tertiary level referral teaching hospital of Jodhpur over a I5-month period. It was a prospective case controlled study in which all deliveries taking place in Umaid hospital during the morning working hours of 8 am to 2 pm were attended by the senior registrar on call (JB) personally and severely asphyxiated babies (Apgar of 7 or less at 5 minutes) were enrolled for the study. Uniformity in neonatal resuscitation protocol and grading of asphyxia according to Apgar at 5 minutes was assured by eliminating observer bias. Every fortnight one non- asphyxiated baby with no known confounding factor believed to alter renal functions such as septicemia, RDS, NEC, major congenital malformations etc. was randomly picked up to serve as control. The enrolled babies were thus divided into two groups- Group A comprised of 70 asphyxiated newborns while group B had 28 healthy babies. Excluded from our cohort were babies with necrotizing enterocolitis, severe septicemia and marked respiratory distress.

On the basis of Apgar score at 5 minutes the asphyxiated babies were further grouped into mild (score of 6 or 7) moderate (score 5 or 4) and severe asphyxia (score 3 or less). All neonates (term or preterm) with clinical features of HIE were staged by Sarnat and Sarnat scoring system(3). All enrolled babies were subjected to an ultrasonography within 24 hours of birth to rule out any congenital malformation of the urinary tract.

Gestational age(4), birth weight, relevant perinatal history, findings on physical examination and systemic signs were recorded on a predesigned pretested proforma. Daily weight recordings were taken on an electronic scale, 24 hours urine output measurement done by applying plastic collection bags and urine examination performed everyday.

Renal function parameters–blood urea, serum creatinine, serum electrolytes, urinary sodium and creatinine were monitored initially within 24 hours of birth and then on day 3 of life. After 3 days those babies having abnormal renal functions had their laboratory parameters monitored every alternate day till recovery. Neonates who developed renal failure were managed conservatively as per the standard hospital protocol. Arterial blood gas analysis, ECG and calculation of fractional excretion of sodium ($FENa^+$) were done as and when required. Criteria adopted for labeling an asphyxiated neonate as having renal failure were urine output <0.5 mL/kg/hour, blood urea >40mg/dL, serum creatinine >1mg/dL, presence of significant hematuria or proteinuria. These criteria were, applied on day 3 of life and any three of the four criteria when fulfilled were considered as indication of renal failure. Mishra *et al.*(5) too had considered oliguria not responding to fluid challenge and/or diuretics, serum creatinine >1.8 mg% or peak BUN >40 mg% or hematuria and/or proteinuria with FENa >2.5% and RFI >3 as indicator of intrinsic ischaemic renal damage. Asphyxiated babies with impaired renal functions were grouped as A_2 and remaining babies from group A with normal renal functions were grouped as A_1. Statistical analysis was performed using the Students' *'t'* test and chi-square test.

Neonates with renal failure were followed up at 1 and 6 months of age to detect any residual abnormalities. Ultrasonic imaging of kidneys was also carried out at point of entry

into study and on day of discharge. Kidney size, echotexture and corticomedullary differentiation were noted. Sonographic scans were repeated at 1 and 6 months of age.

Results

Of the 98 neonates enrolled 66.3% were males and 33.7% females. Mean birth weight in-group A and B were 2.80 ± 0.44 kg and 2.62 ± 0.52 kg respectively. Gestational age wise categorization of babies was evenly matched in the two groups. Apgar score of the 70 asphyxiated babies from group A at 5 minutes was 0-3 in 17 (17.3%), 4-5 in 30 (30.6%) and 6-7 in 23 (23.4%). Of the asphyxiated babies (N = 70) 38 cases (54.25%) had hypoxic ischemic encephalopathy with 12.8% each in stage I and III while 28.5% babies had HIE stage II with 32 babies having no evidence of HIE.

Mean urine output in-group A was 1.28 mL ± 0.36 mL/kg/hour, which was comparable to values of 1.38 mL ± 0.28 mL/kg/hour in the control group (P >0.6). No significant difference in mean urine output was observed in newborn with varying grades of asphyxia. While 12 (17.1%) asphyxiated neonates were showing proteinuria of ++ or more 11.4% had microscopic hematuria and further 11.4% had both proteinuria and hematuria. But in control no baby had hematuria and only 7.1% showed trace to + 1 proteins in their urine.

Blood urea and serum creatinine were significantly higher in asphyxiated babies compared to the control group (P<0.001). (*Table I*). A rising trend in concentration of blood urea and creatinine was observed as HIE staging of neonates progressed and the difference was statistically significant between babies with no HIE and those with HIE stage III (P <0.05, *Table II*). Similar correlation was observed when blood urea and creatinine levels were categorized according to Apgar score at 5 minutes *i.e.*, higher values of urea and creatinine were seen with lower Apgar scores.

It was observed that babies with asphyxia had significantly higher incidence of hyponatremia and the mean serum sodium levels in study group (132.82 ± 5.73mEq/L) was lower than that observed in control group (135.82 ± 3.99 mEq/L, P <0.001). Serum potassium levels were comparable in the two groups (4.51 ± 0.72 mEq/L in group A and 4.35 ± 0.44 mEq/L in group B). Mean fractional excretion of sodium was 0.6 ±

TABLE I–*Urea and Creatinine Levels (mean ± SD) on Day 3 in Study and Control Group*

	Study	Control	*P* value
Blood Urea (mg/dL)			
Preterm	(n = 11) 42.09 ± 25.20	(n = 10) 20.60 ± 4.45	<0.02
Term	(n = 59) 35.72 ± 17.87	(n = 18) 22.72 ± 5.44)	<0.001
Total	35.03 ± 19.05	21.96 ± 5.44	<0.001
Serum Creatinine (mg/dL)			
Preterm	1.34 ± 0.79	0.83 ± 0.26	<0.05
Term	1.08 ± 0.49	0.88 ± 0.26	<0.05
Total	1.13 ± 0.55	0.86 ± 0.23	<0.001

Difference in biochemical parameters between preterm and term babies - Not significant.

TABLE II–*Urea and Creatinine Levels Correlated with HIE Staging.*

HIE Staging of Group A	n	Blood urea (mg/dL) mean ± SD	P values (compared to control)	S. creatinine (mg/dL) mean ± SD	*P* values (A group vs B group)
0	32	28.9 ± l0.3	<0.01	0.9 ± 0.2	>0.1
I	09	41.2 ± 2406	<0.05	1.1 ± 0.4	<0.05
II	20	36.8 ± 23.9	<0.01	1.3 ± 0.8	<0.05
III	09	46.1 ± 24.5	<0.01	1.4 ± 0.6	<0.01
Total	70	35.00 ± 19.0	<0.01	1.1 ± 0.5	<0.001
Control group B	28	21.96 ± 5.0	–	0.86 ± 0.23	–

Stage I compared to stage III: – significant difference (P <0.05).

0.56% in-group A and 0.29 ± 0.27% in-group B which is a highly significant difference. But values of $FENa^+$ do not exceed 1.0 to 2.0 in group A as all babies did not have renal failure. $FENa^+$ levels were higher in neonates with HIE II and III than in the control group while it was comparable in babies of HIE O and I stage with that of control babies.

Thus, of the 70 asphyxiated babies in our study group 37 had normal renal functions (Group A1). A comparison of the biochemical parameters between group A1 and A2 is given in *Table III*. Mean $FENa^+$ levels in-group Al was 0.38 ± 0.31% compared to 0.85 ± 0.67% in-group A2 that is a statistically significant difference. But only 7 babies had $FENa^+$ values of 1 to 2.5 and two babies had values of >2.5.

Majority of asphyxiated neonates had non-oliguric renal failure (26/33-78%) while oliguric failure was seen in (7/33) 21% cases-the mean urine output being 1:494 ± 0.31mL/kg/hour and 0.61± 0.28mL/kg/hr respectively in the 2 groups. Since oliguria was seen in only 6 babies the mean urine output in the study and control group did not show any significant difference.

Babies with oliguric renal failure had higher mortality rate (42.8%) than that seen in the non-oliguric group (7.7%). Of the 33 neonates with ARF 5 (14.1%) expired, 14 (42.1%) improved on day 7-9 and 3 (9.1%) still had abnormal renal function on day 7-9 but this too normalized on follow-up. Renal sonography performed in asphyxiated babies showed abnormalities in 5 (6.6%) cases in form of increased size, altered echotexture and loss of corticomedullary differentiation. Scans were normal in babies of group Al and controls. Of the 5 babies who died four were having HIE grade III and one had HIE grade II.

On follow-up, urine output increased on day 4-6 and was comparable in neonates with different HIE staging, but levels of blood urea and serum creatinine on day 4-6 increased and then declined to normal values by 7-9 days of life in all neonates.

Biochemicals parameters were repeated at 1 to 6 months to detect any residual impairment showed normal parameters except in one newborn who had blood urea of 44mg/dL at 1 month of age but this too normalized later. Sonographic scans were normal in all babies at follow-up.

Discussion

Renal injury in birth asphyxia is a potential

TABLE III–*Biochemical Parameters on Day Three.*

Group	N	Urea (mg%)	Creatinine (mg%)	Na^+ (mEq/L)	K^+ (mEq/L)
AI	37	25.1 ± 10.8	0.80 ± 0.2	133.7 ± 40.1	4.5 ± 0.5
A2	33	46.8 ± 20.2	1.4 ± 4.6	130.2 ± 60.7	4. 5 ± 0.8
B(Control)	28	21.9 ± 0.5	0.8 ± 0.2	135.8 ± 3.9	4.3 ± 0.4

A_1: Asphyxiated babies with no renal failure. A_2: Asphyxiated babies with renal failure.

Comparison of groups

A_1 vs B	Urea: *P* value >0.7; Creatinine *P* >0.6; K^+ *P* >0.l.
	Significant difference in Na+ levels only. (*P* <0.05).
A_2 vs B A_l vs A_2	All parameters except K^+ (urea, creatinine & sodium values) showed significant difference (*P* <0.02).

consequence of adaptive mechanism. Amongst the recognized complications *i.e.*, acute tubular necrosis, renal vein thrombosis and renal failure, ARF is the commonest and carries a poor prognosis and may even result in permanent renal damage in up to 40% of survivors(6).

Urinary output was slightly less in neonates with severe birth asphyxia but it was statistically insignificant when compared with cases of mild and moderate asphyxia. But oliguria has been reported in higher number of neonates by other authors with figures ranging from 25% to 69.2% babies(7-8).

Non-oliguric renal failure is a recognized entity secondary to perinatal asphyxia. Renal parenchymal injury in non oliguric as well as oliguric renal failure is essentially similar but heterogenous response of individual nephron and variable damage to tubular epithelium results in anatomical damage in majority of nephrons leading to reduction in single nephron GFR and decreased tubular fluid flow. But if damage to tubular epithelium is less severe there occurs decrease in fractional reabsorption which exceeds the decrease in single nephron GFR leading to polyurea in non-oliguric renal failure(9).

11.4% of our asphyxiated neonates showed both proteinuria and hematuria and babies with HIE II or III had more urinary anomalies. Proteinuria is disproportionately higher in the neonatal period than it is later in life with levels as high as 240 mg/m^2/d in 1st 48 hours of life. In addition about 10% of neonates will have hematuria detected by dipstick and may have urinary red cell count up to 10 cells/mL(10). Impaired tubular function after asphyxia leads to occurrence of significant tubular proteinuria and qualitative assessment of proteinuria by measuring p2-M-a low molecular weight protein to detect tubular injury has been proposed by various authors(11,12).

Obstruction of tubular lumen and back leak mechanism contributed to increase in urea and creatinine levels in asphyxiated neonates and other authors too noted great correlation between severity of HIE and ischemic damage to the kidneys manifesting as ARF(13).

The capacity of sodium reabsorption is limited and if the load of sodium reaching the DCT increases significantly, reabsorption does not occur proportionately and the

Key Messages

- Birth asphyxia is a significant cause of renal failure in neonates.
- Oliguric renal failure with hyponatremia carries a bad prognosis.

sodium load is excreted in the urine. Other contributing factors to hyponatermia may be occurrence of SIADH secondary to perinatal asphyxia and partial resistance to aldosterone(14). Hyponatremia per se may lead to contraction of intravascular volume further reducing the renal functions(15). The incidence of renal involvement observed in our study (47.14%) compared well with figures of other author(14-15). Sonographic abnormalities were seen in babies with biochemical evidence of renal dysfunction and 3 of them were oliguric. Four out of 5 babies with abnormal sonography expired.

In our study no neonate remained oliguric by day 4-6 of life, which compares well with observations of Pertman, *et al.*(7) who reported transient oliguria on 1st day in 23% of newborns and urine output increased to normal values on 3rd day of life.

A reduction in number of functional nephrons caused by asphyxia and leading to ARF evokes compensatory hypertrophy of the residual nephrons thus leading to improved renal functions in early months of life. But whether subtle defects may persist, can be said only after long term follow-up and one must be cautious in prognosticating these neonates. Brochieback(16) reported that up to 40% of survivors may have decreased creatinine clearance, renal tubular acidosis or concentrating defect. Oliguria, abnormal renal sonographic scan and hyponatermia were noted to be the ominous signs predicting mortality in our study. The limitation of our study has been our inability to check for residual renal tubular dysfunction, BP monitoring, evidence of RTA, urinary concentrating ability, and renal imaging which can provide information on residual subtle defect.

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