Original Research Article

Renal profile of asphyxiated neonates in relation to the severity of asphyxia

Girijanand Jha[1],Saroj Kumar[2*],Samiksha Sharma[3],Binod Kumar Singh[4]

[1]Senior Resident, Department of Pediatrics, N.M.C.H, Patna, Bihar, India
[2]Assistant Professor, Department of Pediatrics, N.M.C.H, Patna, Bihar, India
[3]Senior Resident, Department of Pediatrics, N.M.C.H, Patna, Bihar, India
[4]Professor & HOD, Department of Pediatrics, N.M.C.H, Patna, Bihar, India

Received: 07-01-2021 / Revised: 04-03-2021 / Accepted: 26-03-2021

Abstract

Background and Objectives: Perinatal asphyxia (PA) is a major problem that contributes significantly to neonatal mortality as well as long term morbidity.Due to their unique characteristics, neonatalKidneys are one of the most common organs involved in multiple organ dysfunction caused by asphyxia. Whereas renal complications in perinatal asphyxia have been well studied, literature regarding degree of renal dysfunction in relation to severity of asphyxia is sparse. This study was conducted 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 neonates.**Methodology:** This prospective case control study was conducted over 1 year from July 2019 to June 2020 at NICU of our tertiary care hospital. Consecutively admitted neonates of gestational age >34 weeks with PA formed the study group who were carefully matched with equal number of non-asphyxiated neonates of comparable gestational age, weight & gender. Renal function was assessed by urine output, urine microscopy, biochemical parameters & sonographic findings. **Observation and Results:** 102 asphyxiated neonates were enrolled as cases (group A) in the present study. Of these asphyxiated neonates, 58 (56.9%) had hypoxic ischemic encephalopathy (HIE). Urine output in group A was 1.23 mL ± 0.41 mL/kg/hour which was comparable to 1.31 mL ± 0.39 mL/kg/hour in the control group (P = 0.15). Blood urea and serum creatinine were significantly higher in asphyxiated babies as compared to the control group (P<0.05). Concentration of urea and creatinine increased with progression of the HIE stage. This trend was statistically significant between babies with no HIE and those with HIE stage III (P <0.05). Neonates with asphyxia also had significantly higher incidence of hyponatremia (30.4% vs 10.8%). 44.1% neonates had acute renal failure. Non-oliguric renal failure (29/45, 64.4%) was more common than oliguric renal failure (16/45, 35.6%). Neonates with oliguric renal failure had higher mortality rate. Renal parameters normalized in all survivors by 1 months of age.**Conclusion:** Renal failure is a significant problem in asphyxiated neonates with majority of neonates having non-oliguric renal failure. Severity of renal function abnormality correlates well with degree of asphyxia.

Keywords: Perinatal asphyxia, Hypoxic ischemic encephalopathy, acute renal failure, oliguria

Abbreviations:ARF: acute renal failure; HIE: hypoxic ischemic encephalopathy;PA: perinatal asphyxia; RFT: renal function test; SD: standard deviation.

Introduction

Perinatal asphyxia (PA) is a major problem that contributes significantly to neonatal mortality as well as long term morbidity. This life threatening condition results from lack of oxygen (hypoxia) or perfusion (ischemia) to fetus or newborn that results in multiple organ dysfunction of sufficient magnitude and duration[1]. Its toll can be understood from the fact that it alone contributes to approx 10% of all under five child deaths and approx 28.8% of all neonatal deaths[2]. While almost every organ of the body is affected, the most frequently affected organs are kidneys (50%), central nervous system (28%), cardiovascular (25%) and pulmonary system (23%). Kidneys are one of the most important organs commonly involved in the multiple organ dysfunction caused by perinatal asphyxia[3]. Renal injury in perinatal asphyxia is a potential consequence of an adaptive mechanism, however such a mechanism is not always protective. Renal manifestations of asphyxia include hematuria, acute tubular necrosis, renal vein thrombosis etc. Amongst the recognized complications, Acute Renal Failure (ARF) is the most common and carries a poor prognosis. As nephrons are very sensitive to hypoxia or inadequate perfusion, renal insufficiency may begin within minutes of a hypoxic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis. Early recognition of such a damage is important in neonates with HIE to maintain appropriate fluid and electrolyte status so as to provide a stable biochemical milieu. However,diagnosis of renal failure is difficult in neonates as many of the established clinical and biochemical parameters are unreliable in this age group. Though with prompt recognition and management majority of neonates improve, upto 30% of survivors may develop permanent renal damage[4].Whereas renal complic-ations in perinatal asphyxia have been well studied, literature regarding degree of renal dysfunction in relation to severity of asphyxia is sparse. Only few studies have specifically focused on renal derangement as the severity of asphyxia progresses[5,6]. In the absence of a proper perinatal record, it is very difficult to diagnose and grade asphyxia after delivery. There is pressing need to identify neonates who are at a high risk of suffering from renal failure or multi-organ dysfunction. It is therefore prudent to keep a high index of suspicion of renal dysfunction in asphyxiated neonates. Based on this background we conducted the present study to study renal impairment in perinatal asphyxia in detail.

**Correspondence*
Dr. Saroj Kumar
Assistant Professor, Deptt of Pediatrics, N.M.C.H, Patna, Bihar, India
E-mail: drgiriped@gmail.com

Aim and objectives:

Aim: To study renal profile of asphyxiated term neonates in relation to severity of asphyxia.

Objectives:i. To study the incidence of renal dysfunction in asphyxiated neonates.

ii. To study the relationship between severity of renal failure and Apgar score as well as HIE grade of asphyxiated neonates.

Methodology

Study setting: N.I.C.U of Deptt of Pediatrics N.M.C.H Patna, Bihar, India

Study duration: 1 year, from July 2019 to June 2020.

Study design: prospective case controlled study.

Inclusion criteria: In the present study we included consecutively admitted neonates of gestational age >34 weeks with perinatal asphyxia as cases. Perinatal asphyxia was defined as failure to initiate and sustain breathing. If available, an APGAR of 6 or less at 1 minutes of age was taken an indicative of asphyxia. For every such neonate included as "case" one non- asphyxiated baby of similar gestational age and weight 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". Gestational age and gender wise categorization of babies was evenly matched in the two groups. The enrolled babies were thus divided into two groups- Group A comprised of asphyxiated newborns (cases) while group B had healthy neonates (controls).

Exclusion criteria: Neonates with confounding factors which are believed to alter renal function such as septicemia, respiratory distress syndrome, necrotizing enterocolitis, major congenital anomalies and administration of nephrotoxic drugs either to baby or to mother were excluded from the study. Neonates whose antenatal USG scans had any structural abnormality of fetal kidney were also excluded.

Data Collection: After obtaining written informed consent, we enrolled participants in this study. Information regarding perinatal events, baseline characteristics, detailed relevant history, clinical examination, admission diagnosis, maternal renal functions (serum urea and serum creatinine) prior to delivery was recorded in a structured proforma. We classified such neonates on the basis of APGAR score at 5 minutes into mild (APGAR score of 6 or 7) moderate (APGAR score 5 or 4) and severe asphyxia (APGAR score 3 or less). All neonates with clinical features of HIE were staged by Sarnat and Sarnat scoring system[7].Renal ultrasonography was done as soon as clinical condition stabilized to rule out any congenital malformation of the urinary tract. 24 hours urine output measurement was done by applying plastic collection bags around genitals or aseptic bladder catheterization. Renal function tests (RFT)–blood urea, serum creatinine, serum electrolytes, urinary sodium and creatinine were monitored initially within 24 hours of birth or admission (whichever was earlier) and then again on day 3 of life. Neonates with abnormal renal functions persisting on day 3rd and/or beyond had their laboratory parameters monitored every alternate day till recovery. Neonates who suffered from renal failure were managed conservatively as per standard hospital protocol. Other relevant lab investigations including ABG were done as per clinical scenario. Asphyxiated neonates with impaired renal functions were grouped as A2 and remaining babies from group A with normal renal functions were grouped as A1. Neonates with deranged baseline RFT as per age reference values in presence of normal maternal RFT were assumed to have primary disease of kidney.In the present study we defined acute renal failure as:

- Ser Creatinine (SCr) rise ≥0.3 mg/dl or ≥ 50% increase from baseline over 48 hours, OR

-Plasma creatinine more than 1.5 mg/dl for at least 48 hours if mother's renal function was normal, OR

- urine output less than 1 mL/kg/hr for 24 hours after first day of life.

Statistical analysis: Pertinent data was recorded, tabulated and entered in Microsoft excel sheet, and then analyzed by using statistical software "SPSS ver.20®.Variables were expressed as mean, standard deviation and percentiles. Dichotomous variables were compared using Chi-square test whereas continuous variables were compared using Student t-test. P-value<0.05 was taken as significant.

Observation and results

Over the study period, we enrolled 102 neonates as cases (group A) in the present study. An equal number of carefully matched neonates were chosen as controls (group B). Male: female ratio was 1.7:1. Mean weight on admission in-group A (cases) and B (controls) were 2.87 ± 0.42 kg and 2.64± 0.48 kg respectively, the difference wasn't statistically significant (p value=0.4).APGAR score of the asphyx-iated babies in group A at 5 minutes was 0-3 in 27 (26.5%), 4-5 in 43 (42.16%) and 6-7 in 32 (31.4%) neonates. Of these asphyxiated neonates (n=102), 58 neonates (56.9%) had hypoxic ischemic encephalopathy (HIE). Among these asphyxiated neonates, stage I HIE was seen in 22.4% (n=13), stage II in 36.2% (n=21) while 41.4% (n=24) babies had HIE stage III.

Mean urine output in-group A was 1.23 mL ± 0.41 mL/kg/hour, which was comparable to values of 1.31 mL ± 0.39 mL/kg/hour in the control group (P = 0.15). No significant difference in mean urine output was observed in newborn with varying grades of asphyxia. While 16.7% (n=17)of asphyxiated neonates had proteinuria of 2+ or more, 11.8% (n=12) had microscopic hematuria; further 8.8% (n=9) hadboth proteinuria and hematuria. Whereas in controlgroup, no infant had hematuria and only 8.8% (n=9) showedtrace to + 1 proteins in their urine.Blood urea and serum creatinine weresignificantly higher in asphyxiated babiescompared to the control group (P<0.05) as shown below in table 1.

Table 1: Blood urea & serum creatinine levels (mean ± SD) on 3rd day in study and control Group

Parameters	Asphyxiated neonates (n=102)	Controls (n=102)	P value
Blood urea in mg/dl			
Preterm	(n = 14) 43.12 ± 22.03	(n = 14) 22.56 ± 8.12	0.003
Term	(n = 88) 36.53 ± 16.44	(n = 88) 21.61 ± 7.33	<0.001
Total	(n=102) 35.94 ± 21.26	(n=102)22.11 ± 7.09	<0.001
Serum creatinine in mg/dl			
Preterm	(n=14) 1.39 ± 0.85	(n=14) 0.79 ± 0.27	0.02
term	(n=88) 1.15 ± 0.63	(n=88) 0.84 ± 0.24	<0.001
Total	(n=102) 1.17 ± 0.61	(n=102) 0.81 ± 0.22	<0.001

In the present study, we noticed that concentration of urea and creatinine increased withprogression of HIE stage of the neonates. This trend was also statistically significant between babies with no HIE and those with HIE stage III (P <0.05) as shown in Table II. Similar association was observed when blood urea and creatinine levels were studied in relation to low APGAR score at 5 minutes: higher value of urea and creatinine was seen with lower APGAR score. We also observed that neonates with asphyxia had significantly higher incidence of hyponatremia (30.4% vs 10.8%). Even the mean serum sodium levels in asphyxiated neonates (132.14 ± 4.98mEq/L) was lower than that observed in control group (136.53 ± 5.72 mEq/L, P <0.001). Serum potassium levels were comparable in the two groups (4.39 ± 0.69 mEq/L in group A and 4.31 ± 0.56 mEq/L in group B, P= 0.36).

Table 2: Comparison of renal parameters as per HIE severity on day 3 of life

HIE Stage	Number	Blood urea (mg/dl)	*P value	Ser. Creatinine (mg/dl)	*P value
0	44	25.94 ± 8.1	0.005	0.92 ± 0.27	0.01
I	13	31.26 ± 12.6	<0.001	1.12 ± 0.43	<0.001
II	21	36.23 ± 16.3	<0.001	1.3 ± 0.8	<0.001
III	24	42.71 ± 23.9	<0.001	1.4 ± 0.6	<0.001
Total	102	35.94 ± 21.26	<0.001	1.17 ± 0.61	<0.001
Control group	102	22.11 ± 7.09	----------	0.81 ± 0.22	----------

* P value arrived at by comparing with the control group.

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

Renal failure in asphyxiated neonates: Of the 102 asphyxiated babies, 57 had normal renal functions (Group A1) and 45 neonates had acute renal failure (Group A2). Most of the asphyxiated neonates had non-oliguric renal failure (29/45, 64.4%) while oliguric failure was seen in (16/45, 35.6%) cases. Mean urine output was 1.42 ± 0.38mL/ kg/hour and 0.57± 0.26mL/kg/hr respectively in the non-oliguric and oliguric group respectively.

Mortality and outcome: Overall mortality in the asphyxiated neonates was 22 (21.6%). Out of the 45 neonates with ARF, 14 died (31.1%). Neonates with oliguric renal failure had higher mortality rate (n=7, 43.8%) than that seen in the non-oliguric group (n=7, 24.1%). Of the 45 neonates with ARF, 27 (60%) improved by day 10 while 4 (8.9%) had abnormal renal function by day 10. However, this too normalized by 4 weeks during follow-up visits. Urine output gradually increased by day 5 and was comparable in neonates with different HIE staging. Renal sonography performed in those with ARF showed abnormalities in 7 (15.6%) cases in form of increased size, altered echotexture and loss of corticomedullary differentiation. Follow-up scans were normal in all such babies.

Table 3: Comparison of renal parameters as per severity of renal injury

Group	Number	Urea (mg/dl)	Creatinine (mg/dl)	Ser Na^+ (mEq/L)	Ser K^+ (mEq/L)
A1	57	23.6 ± 7.18	0.87 ± 0.25	136.7 ± 4.92	4.43 ± 0.59
A2	45	49.8 ± 23.7	1.5 ± 0.72	131.1 ± 6.19	5. 5 ± 0.74
Control group (Group B)	102	22.11 ± 7.09	0.81 ± 0.22	136.53 ± 5.72	4.31 ± 0.56

A1: Asphyxiated neonates without renal failure. A2: Asphyxiated neonates with renal failure.

Comparison of groups

A1 vs B: No statistically significant difference in urea, creatinine, Na^+ or K^+ level.

A2 vs B:Statistically significant difference in all parameters.

Al vs A2:Statistically significant difference in all parameters.

Discussion

Renal injury in birth asphyxia is a potential consequence of adaptive mechanisms. Infact kidney are the most common organ involved in perinatal asphyxia. In the present study we intended to study the renal status of asphyxiated neonates. 102 asphyxiated neonates formed the study group who were carefully matched with equal number of non-asphyxiated neonates of comparable gestational age, weight and gender. Of the asphyxiated neonates, (56.9%) had hypoxic ischemic encephalopathy (HIE). This is considerably higher than the usual notion that around 30% neonates with asphyxia suffer from HE[8].However, as our is a tertiary care level study, this might be probably a reflection of differential rate of admission of sicker neonates in our hospital. Mean urine output in asphyxiated and non-asphyxiated neonates was comparable. Also, there was no significant decrease in urine output in neonates asseverity of asphyxia progressed. Blood urea and serum creatinine were significantly higher in asphyxiated babies compared to the control group. This is comparable to the study of Gupta et al[9] which was conducted in an Indian tertiary care level teaching hospital. We also found that concentration of urea and creatinine increased with progression of HIE stage of the neonates. Unlike urine output, this trend was statistically significant between babies with no HIE and those with HIE stage III. Similar to our findings, kidney functions studied by JayaswalA et al[10] in 40 neonates of different HIE stages on day 3 and 5 of age showed that as the HIE stage increased biochemical derangement worsened.Acute renal failure was seen in 57 (53.8%) neonates.Similar incidence of renal involvement has been reported by researchers worldwide as well as India[11]. However, we also found thatsignificantrenal injury can occur in neonates who are non oliguric. In the present study, nearly 2/3rd of neonates with ARF were non oliguric which was comparable to the findings of Aggarwal A et al[12].Mohan PV and Pai MP have also reported that 72% of neonates suffering from asphyxia had either oliguric or non oliguric renal failure[13]. Levels of urea and creatinine were significantly higher as the severity of HIE progressed. Other studies too found similar correlations of biochemical parameters with the severity of HIE. In their study Jayshree et al reported that there was significantly higher incidence of ARF in stage 2 and 3 as compared to stage 0 and 1[14].Non-oliguric renal failure is a recognized entity secondary to perinatal asphyxia. Glomerular injury in non oliguric as well as oliguric renal failure is essentially similar but variable damage to tubular epithelium results in oliguric renal failure in some and non oliguric renal failure in others, the latter being more common in asphyxiated neonates.8.8% of our asphyxiated neonates showed both proteinuria and hematuria and neonates with HIE II or III had more urinary anomalies. Impaired tubularfunction after asphyxialeads to occurrence of significant tubular proteinuria and qualitative assessment of proteinuria by measuringp2-M-a low molecular weight protein to detecttubular injury has been proposed by various authors [15].As the capacity of sodium reabsorption islimited, reabsorption of Na^+does not occur proportionately that leads to excretion of the sodium load in urine. SIADH may also play a role here. This might explain the significantly lower mean sodium levels in asphyxiated group as compared to the controls in our study. In our study no neonate remained oliguric by day 5 of life, which is comparabletothe observation of Perlman, et Al[16] whoreported that oliguria was transient during the first 48 hours of and urine output increased to normal values by 3rd day of life.The strength of our study is that we compared renal dysfunction in different stages of HIE and also monitored renal functions till discharge and during follow up visits.As we enrolled neonates with normal maternal serum urea and creatinine (prior of delivery), the confounding effect ofmaternal influence on neonatal RFT was removed. We also excluded neonates with an abnormal renal sonogramto eliminate primary diseases of kidney.

Conclusion

Neonatal kidneys are one of the most common organs to bear the brunt of perinatal asphyxia.Incidence of renal injury increases as the severity of asphyxia worsens. Overall,neonates with HIE stage III are more likely to suffer from renal impairment as compared to stage I or II. As non-oliguric renal failure is the commonest type of renal failure in such neonates, one must not be misguided by such "adequate" urine output and a high index of suspicion should be

always kept in mind while managing neonates with asphyxia. Renal function derangement in perinatal asphyxia can be used as an early predictor of severity of disease that would help in deciding about the optimal quality of care required for such unfortunate neonates.

Limitations

First limitation is that we did not take umbilical cord blood sample to see metabolic or mixed academia for labeling neonates as perinatal asphyxia as recommended by the American Academy of Pediatrics. As long term follow up of these neonates was not done, we couldn't assess the correlation between severity of renal dysfunction and neurodevelopmental outcome.

References

1. Perlman JM, Tack ED, Shackelford G,Acute systemic organ injury in term infants after asphyxia. Am J Dis Child. 1989;143:617-20
2. National Neonatology Forum of India. National neonatal perinatal database report for 2002-2003. Available on**Error! Hyperlink reference not valid.** (last accesssed on 16 June 2020).
3. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian pediatrics. 2005;42(9):928-31
4. Stapleton FB, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. Pediatric Nephrology. 1987;1(3):314-20
5. El-Gamasy MA, Alarabawy R. Relation of serum creatinine to Sarnat scoring and brain computerized tomography of neonates with hypoxic ischemic encephalopathy. A single-center experience. J PediatrNeurosci. 2018;13:437-42.
6. El-Gamasy MA, Abdelmageed MM, Fakhreldin AR, Mehrez MM, Nassar MA, Alarabawy R. Correlation of Renal Function with Severity of Hypoxic Ischemic Encephalopathy (HIE) in Egyptian Full Term Neonates. NeonatPediatr Med. 2018; 4 (2): 157-60.
7. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress-A clinical and electroencephalographic study. Arch Neuro. 11976; 33: 696-705
8. Kimberly A. Allen, Debra H. Brandon. Hypoxic Ischemic Encephalopathy:Pathophysiology and Experimental Treatments. Newborn Infant Nurs Rev. 2011; 11(3): 125–133
9. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr. 2005;42(9):928-34
10. Jayaswal A, Chaurasiya OS, Sethi RS. Renal dysfunction in perinatal asphyxia & its correlation with APGAR score and hypoxic ischemic encephalopathy stage. People's Journal of Scientific Research. 2016;9(2):56-60.
11. Chacham S, Nagasravani J, Reddy UN. Acute renal failure in neonates with perinatal asphyxia and its correlation with HIE staging: a prospective case control study. J NeurolNeurobiol. 2016;2(2):1-6
12. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. Journal of Tropical Pediatrics. 2005;51(5):295-99.
13. Mohan PV, Pai MP. Renal insult in asphyxia neonatorum. Indian Pediatr. 2000;37(10):1102-06.
14. Jayashree G, Dutta AK, Sarna MS, Saili A. Acute renal failure in asphyxiated newborns. Indian Pediatr. 1991;28(1):19-23.
15. Willis F, Summers J, Minutillo C, Hewitt I. Indices of renal tubular function in perinatal asphyxia. Arch Dis Child (Fetal Neonatal Ed). 1997; 77: F57-F60.
16. Perlman JM, Tack ED. Renal injury in the asphyxiated newborn infant: Relationship to neurogenic outcome. J Pediatr. 1998; 113: 875- 79.

Conflict of Interest: Nil
Source of support:Nil