Original Article

Impairment of Renal Function in Perinatal Asphyxia with Hypoxic Ischemic Encephalopathy in Term Neonates

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Abstract

Background: *Perinatal asphyxia is a major cause of neonatal morbidity and mortality worldwide including in Bangladesh. It causes damage to almost every tissue and organ of the body. In kidneys, renal insufficiency may occur promptly even within 24 hours of asphyxia. So, renal function assessment is essential for accurate management of metabolic derangement in neonates as prolonged hypoxic ischemic episode can lead to irreversible cortical necrosis with onset of acute renal failure.*

Objectives: *To find out renal impairment and to measure serum creatinine, serum electrolyte and eGFR, Also to compare biochemical parameters level and determine the frequency of AKI among the asphyxiated neonates with HIE.*

Materials and Methods: *This cross-sectional study was conducted in the neonatal care unit of Sir Salimullah Medical College Mitford Hospital, Dhaka. A total of 70 term neonates suffered from perinatal asphyxia with different stages of Hypoxic ischaemic encephalopathy. A 'p' value <0.05 was considered as statistically significant.*

Results: *Among 70 term neonates having HIE, it was observed that 62.9% neonates had moderate birth asphyxia followed by mild (28.6%) and severe (8.6%). Newborns with SGA (71.4%) had more renal impairment than AGA. Among biochemical variables Blood urea and serum creatinine were high and eGFR was low in stage Π. Among electrolytes, hyponatremia was present in 24.3% of cases and more in stage Π, and hyperkalemia was present in 21.4% of cases and more in stage Ш. AKI was found in 18.6% of cases, Risk (stage 1) was 77%, Injury (stage Π) was 15.3% and Failure (stage 3) was 7.7 %.*

Conclusion: *Renal impairment was found in 18.5% of term asphyxiated neonates with HIE according to pRIFLE and AKIN criteria and Biochemical parameters showed no significant changes between different stages of HIE.*

Key words: *Perinatal asphyxia, Sarnat Staging of Hypoxic ischemic encephalopathy, Term Neonates, eGFR, Renal impairment.*

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Introduction

World Health Organization (WHO) has defined perinatal period-that starts at 22 completed weeks of gestation and ends 7 completed days after birth. Also defined Perinatal asphyxia is "Failure to initiate and sustain breathing at Birth".[1] Perinatal asphyxia is an insult to the fetus or newborn infant due to lack of oxygen (Hypoxia) and or lack of perfusion (Ischemia) to various organs, which will manifest as difficulty in establishing spontaneous respiration evident by delayed cry after birth, at least for 1 minute (Khan 2011). WHO reports that approximately 1 million children die worldwide every year from the diagnosis of perinatal asphyxia.[2] It has an incidence of 6 per 1,000 live full-term births and represents the third most common cause of neonatal death (23%) after preterm birth (28%) and severe infections (26%).[3]

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Perinatal asphyxia is about 1 to 1.5% of live births in most centers and is inversely related to gestational age and birth weight.[1] According to the Bangladesh Demographic and Health Survey (BDHS) 2017 report, it is the second (20.5%) main cause of neonatal mortality; possible serious infection (24.3%) is the top cause.[4] According to the World Health Organization (WHO), the incidence of birth asphyxia is around 3% that is from 130 million newborns each year globally, around 4 million develop birth asphyxia, and from asphyxiated babies around 1.2 million die and the same number develop severe consequences, such as epilepsy, cerebral palsy, and developmental delay. The overall incidence of perinatal asphyxia is about 6% in developing countries.[3]

According to a study done in Nepal incidence was 2.9 per 1000 live born of whom 20% had severe (Apgar score: 1-3) and 80% moderate birth asphyxia (Apgar score: 4-6). United Nations Children's Fund(UNICEF) report that the under-five mortality rate in Bangladesh in 1990 was 144 per 1,000. But in 2015, the rate is 38 per 1,000 and the child mortality rate across the world was 53 percent, over the same time frame. About two-third of this high mortality in Bangladesh is due to perinatal asphyxia.[5]

It can cause damage to almost every tissue and organ of the body; the most vulnerable ones are central nervous system (72%), followed by kidneys (42%), cardiovascular (29%), gastrointestinal tract (29%) and pulmonary (26%).[1,6,7] It can lead to multi organ dysfunction and a redistribution of cardiac output to maintain cerebral, cardiac and adrenal perfusion while potentially compromising renal, gastrointestinal, and skin perfusion.[7,8]

Kidneys are susceptible to oxygen deprivation. Renal insufficiency may occur promptly even within 24 hours of asphyxia.[9] Prolonged hypoxic-ischemic episode can lead to irreversible cortical necrosis with the onset of acute renal failure (ARF). Renal failure refers to temporary or permanent damage to the kidneys that results in loss of normal kidney function. It may be acute or chronic.[6] Acute renal failure in the newborn has been defined as urine output less than 0.5ml/kg/hour, blood urea more than 40 mg and serum Creatinine more than 1 mg %.[9]

AKI is characterized by a sudden impairment of renal function that results in altered fluid, electrolyte, and acid base balance.[10] Acute Kidney injury (AKI) was noted in 56% of cases. Serum parameters like urea, creatinine, sodium and potassium has better correlation with the renal function as compare to urine parameters.[11] Early recognition of renal failure is essential in neonates with hypoxic ischemic encephalopathy (HIE) to facilitate appropriate fluid and electrolyte management as stable biochemical milieu is vital.[9] Renal failure has also been found to correlate with mortality and long term neurological outcome of asphyxiated babies.[7,12,13] For early prediction of renal injury, markers of renal injury (i,e. S. Electrolytes, S.Creatinine, FeNa, and RFI) are more sensitive and specific in the determination of indices of renal function.[14,15]
Evaluations of blood urea and serum creatinine levels are the tests, most frequently use to assess renal injury caused by perinatal asphyxia. Currently, these indicators are not consider helpful to the early identification of renal damage. In fact, they reflect the glomerular damage and the consequent reduction of glomerular filtration rate (GFR), that occurs at least 24 hours after the hypoxic insult and when about 50% of nephrons are compromise.[6]

The diagnosis of renal dysfunction in neonates is however difficult because the routine clinical and biochemical parameters are affected by many non-renal factors and maternal parameters. Calculated renal indices may also be affected by the difficulty in collecting urine samples.[16] At present, more useful markers of kidney injury are available.[17] Serum creatinine as a marker of GFR. Renal function in neonate is doubtful, because it remains raised and variable during the1st month of life.[18]

Materials and Methods

A hospital-based cross-sectional study was conducted in the neonatal care unit, Department of Neonatology, Sir Salimullah Medical College and Mitford Hospital, Dhaka from September, 2019 to August, 2020 approved by Ethical committee. Total 70 term neonates suffered from PNA with HIE were included in this study fulfilling the inclusion criteria. All term neonate with perinatal asphyxia evident by failure to initiate and sustain breathing at birth, delayed cry after birth at least for one minute and term newborn showing the neuro behavioral signs of HIE. For diagnosis of renal impairment serum creatinine, serum electrolyte and blood urea & eGFR was measured. For acute kidney injury, pRIFLE (Paediatric- Risk –Injury- Failure-Loss-End stage) and AKIN (Acute Kidney Injury Network) was proposed in order to define and stratify the severity of acute kidney injury (AKI). A written informed consent was taken from parents. The sample size was calculated using the formula. Data was analyzed into computer by SPSS version 23.0. Data was compared by Chi-square test for qualitative variables and ANOVA test for quantitative variables where was applicable. A 'p' value <0.05 was considered as statistically significant.

Results

Among 70 term neonates having HIE, it was observed that male was predominant (65.7%) than female (Figure 1). Majority (90%) newborns birth weight was >2500 gm (AGA) and rest (10%) of the newborn was SGA (<2500gm). Mean birth weight was 2773.57gm ± 337.80 (2100-3500 gm) (Table I). 62.9% neonates had moderate birth asphyxia followed by mild (28.6%) and severe (8.6%) (Figure 2) and all neonates passed urine within 24 hours of birth (Table II). Newborn with SGA (71.4%) had more renal impairment than AGA (Table III). Among biochemical variables percentage of blood urea, serum creatinine and eGFR were high (Table IV). Blood urea and serum creatinine were high in stage Π and eGFR was low in stage 2(Table V & VI). Among electrolytes, hyponatremia was present in 24.3% cases and hyperkalemia was present in 21.4% cases, hyponatremia was more in stage Π and hyperkalemia in stage Ш (Table VII). AKI was found in 18.6% cases, Risk (stage 1) was 77%, Injury (stage Π) was 15.3% and Failure (stage Ш) was 7.7 % (TableVIII &IX).

Figure 1: Distribution of asphyxiated neonates according to sex (N=70)

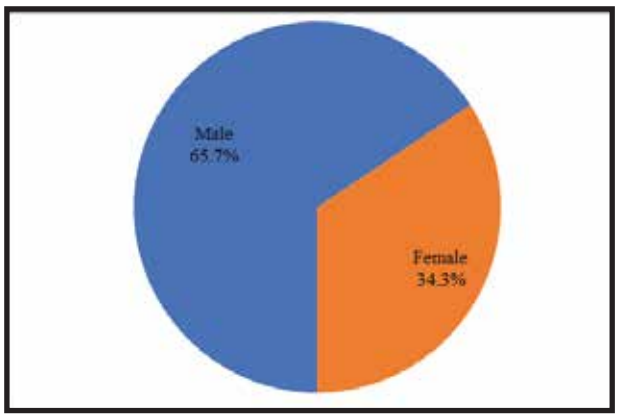

Figure 1 shows the distribution of asphyxiated babies by sex. Male was more in number, 46 (65.7 %) than female, 24 (34.3 %).

Table I: Distribution of the neonates according to birth weight (N=70)

Birth weight (gm)	Frequency (n)	Percentage (%)
<2500 gm (SGA)	7	10.0
≥2500 gm (AGA)	63	90.0
Mean ± SD (Min- Max)	2773.57 ± 337.80 (2100- 3500)	

Table I shows the distribution of the neonates according to birth weight. Among all, majority 63 (90.0%) had birth weight ≥ 2500gm (AGA) and rest 7 (10.0%) of babies birth weight was <2500 gm (SGA)

Figure 2: Distribution of neonates according to HIE staging (N=70)

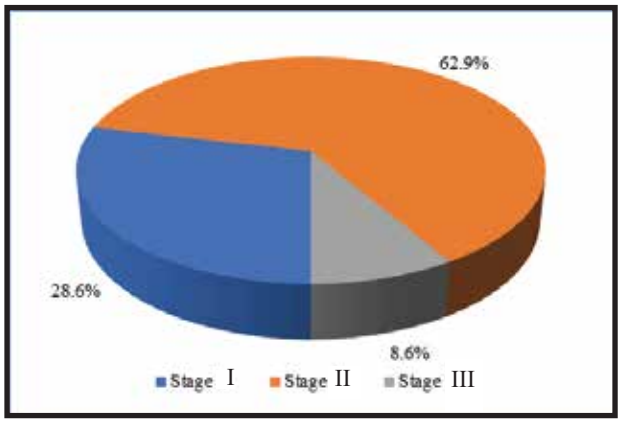

Figure 2 shows that majority were in stage Π (62.9%) followed by stage I (28.6%) and stage III (8.6%).

Table II: Distribution of the neonates according to HIE staging and time of first urination after birth (N=70)

Neonatal variables	Frequency (n)	Percent (%)
HIE stages		
○ Stage 1	20	28.6
○ Stage Π	44	62.9
○ Stage III	6	8.6
First urination after birth (hours)		
○ <24	70	100.0
○ 24-48	0	0
○ > 48	0	.0
Mean ± SD (Min -Max)	8.79 ± 3.20 (4.00 -24.00)	

Table II reveals that among the 70 neonates, maximum, 44 (62.9%) neonates had HIE stage Π, 20 (28.6%) had stage 1 and rest 6 (8.6%) had stage III. All 70 (100%) newborn passed urine <24 hours of birth .It was highly statistically significant. Mean (±SD) duration of passing urine was 8.79 ± 3.20 (4.00-24.00).

Table III: Association of birth weight and gestational age with renal impairment (N=70)

Birth weight	Renal impairment		P value*
	Present	Absent	
SGA	5 (71.4)	2 (28.6)	<0.05
AGA	8 (12.7)	55 (87.3)	

*Fisher's Exact test was done to measure the level of significance.

Table III suggests that among SGA, 5(71.4%) cases and among AGA, 8(12.7%) cases had renal impairment. P value is statistically significant (p<o.o5).

Table IV Distribution of neonates according to Renal function test (N=70)

Investigation variables	Frequency (n)	Percent (%)
Blood urea level (mg/dl)		
o <40	66	94.3
o >40	4	5.7
Mean ± SD (Min - Max)	26.43 ± 11.27 (7.00	- 65.00)
Serum creatinine level (mg/dl)		
o ≤1	59	84.3
o >1	13	18.6
Mean ± SD (Min - Max)	0.78 ± 0.33 (0.20	- 2.00)
eGFR (ml/min/1.73m ^{2})		
o ≤20	9	12.9
o >20	61	87.1
Mean ± SD (Min - Max)	34.38 ± 16.93 (11.00	- 112.00)

Among investigation variable table IV suggests that majority neonates 66 (94.3%) had blood urea ≤40mg/dl, mean blood urea level 26.43 ± 11.27 (7.00-65.00), serum creatinine <1 mg/dl was 59(84.3%), mean value was 0.78 ± 0.33 (0.20-2.00) and eGFR >20 ml/min was found in 61(87.1 %) cases, mean value was 34.38 ± 16.93 (11.00-112.00).

Table VI: Comparison of Renal function test and serum electrolytes with HIE staging (N=70)

Investigation variables	HIE stages			P value
	Stage 1	Stage Π	Stage ΙΙΙ	
Blood urea level (mg/dl)	24.68 ± 7.32	27.13 ± 12.26	27.17 ± 15.43	0.717
Serum creatinine (mg/dl)	0.72 ± 0.30	0.82 ± 0.36	0.72 ± 0.14	0.419
eGFR (ml/min/1.73m²)	37.83 ± 18.34	32.97 ± 17.26	33.25 ± 6.97	0.566
Serum electrolytes (mmo				
o Na	138.96 ± 6.49	138.05 ± 5.59	142.17 ± 7.41	0.286
o K	4.47 ± .70	4.87 ± .87	5.52 ± 1.22	<0.05
o Cl	100.69 ± 3.62	99.52 ± 6.08	101.83 ± 5.31	0.516
o HCO 3	22.00 ± 3.55	23.01 ± 3.09	22.83 ± 3.25	0.514

ANOVA test was done to measure level of significance. (Data was expressed as Mean ± SD.)

Table VI shows among the 70 asphyxiated neonates mean blood urea was 27.17 ± 15.43 in stage III, mean serum creatinine was 0.82 ± 0.36 in stage Π and mean eGFR was 37.83 ± 18.34 in stage 1 and P values was significant (p<0.05) among mean electrolyte values of different stages.

Table V: Comparison of biochemical variables with HIE stages (N=70)

Investigation variables	HIE stage			p-value *
	Stage 1	Stage Π	Stage Ш	
Blood urea level (mg/dl)				
o ≤40	20 (30.3)	41 (62.1)	5 (7.6)	0.266
o >40	0 (0.0)	3 (75.0)	1 (25.0)	
Serum creatinine (mg/dl)				
o ≤1	18 (30.5)	35 (59.3)	6 (10.2)	0.308
o >1	2 (18.2)	9 (81.8)	0 (0.0)	
eGFR (ml/min/1.73m^2)				
o ≤20	2 (22.2)	7 (77.8)	0 (0.0)	0.497
o >20	18 (29.5)	37 (60.7)	6 (9.8)	
Serum electrolyte				
Na (mmol/L)				
o <135	5 (29.4)	11 (64.7)	1 (5.9)	0.902
o 135-145	12 (26.7)	30 (66.7)	3 (6.7)	
o ≥145	3 (37.5)	3 (37.5)	2 (25.0)	
K(mmol/L)				
o <3.5	0	0	0	
o 3.5-5.5	18 (32.7)	34 (61.8)	3 (5.5)	0.1.5
o >5.5	2 (13.3)	10 (66.7)	3 (20.0)	
Cl (mmol/l)				
o Normal (98-107)	15 (31.3)	28 (58.3)	5 (10.4)	0.475
o Abnormal	5 (22.7)	16 (72.7)	1 (4.5)	
HCO 3 (mmol/L)				
o Normal (22-28)	4 (16.0)	18 (72.0)	3 (12.0)	0.202
o Abnormal	16 (35.6)	26 (57.8)	3 (6.7)	

*A Chi-square test was done to measure the level of significance.

Table V shows among biochemical variables blood urea & s.creatinine are more in stage Π, eGFR is low in stage Π. Regarding s.electrolyte hyponatremia & hyperkalemia was more in stage Π.

Table VII: Level of serum electrolytes among asphyxiated neonates (N=70)

Serum electrolyte	Frequency (n)	Percent (%)
Na		
o <135	17	24.3
o 135-145	45	64.3
o ≥145	8	11.4
K		
o <3.5	0	0
o 3.5-5.5	55	78.6
o >5.5	15	21.4

Table VII shows among the electrolytes hyponatremia (<135) present in 17 (24.3%) cases and hypernatremia (>145) present in 8(11.4%) cases. Hyperkalemia (>5.5) present in 5(7.1%) cases and the differences of hyperkalemia were highly statistically significant.

Table VIII: Distribution of asphyxiated neonates according to AKI by pRIFLE criteria (N=13)

RIFLE	Frequency	Percent
Risk	10	77.0
Injury	2	15.3
Failure	1	7.7
Loss	-	-
End - stage	-	-

pRIFLE- paediatric -Risk-Injury-Failure –Loss-End Stage Kidney Disease.

Table VIII shows AKI of asphyxiated neonates according to pRIFLE criteria revealed that 10(77%) was in risk, 2(15.3%) was in renal injury and only 1(7.7%) was in renal failure. So, this table suggests that Asphyxia causes renal impairment.

Table IX: Distribution of asphyxiated newborn according to AKI by AKIN criteria (N=13)

AKIN	Frequency	Percent
Stage 1	10	77.0
Stage Π	2	15.3
Stage ΙΙΙ	1	7.7

AKIN -Acute kidney injury network

Table IX demonstrate AKI of asphyxiated neonates according to AKIN criteria revealed that 10 (77%) was in stage 1, 2(15.3%) was in stage Π, 1(7.7%) was in stage ΙΙΙ.

Discussion

This cross sectional study carried out with an aim to observe the effect of perinatal asphyxia on renal function of term neonates. In this study, it is observed that male (65.7%) was predominant than female 24(34.3%). Shrikhande et al showed male predominant (84) in his study.[19] Gupta et al and Vandana et al also showed male predominant in their study which was consistent with this study.[9,20] In this study ,among asphyxiated newborns Hypoxic ischemic encephalopathy (HIE) stage 2 that is moderate was more 62.9% followed by mild 28.6 % and severe 8.6% which was consistent with the study of Gopal et al.[21] showed that 50% in stage 2 followed by stage 1 & stage 3. It was observed that 70 newborns passed urine within 24 hours of birth. The mean first urination time was 8.79 ± 3.20 (4.00-24.00). Aggarwal et al.[22] showed his study that oliguria >24 hours had a moderate positive predictive value which is not consistent with this study.

In this study it was observed that blood urea >40 mg/dl present in 4 (5.7%) cases which was not significant. Gupta et al. showed mean blood urea was 35.72±17.87 and p value was highly significant. Another study by Aggarwal et al. done that matched with Gupta,s study that differ with my study.[9 ,22]

In present study it was observed that among 70 (100%) asphyxiated newborn serum creatinine >1 mg/dl 11 (15.7%), mean value was 0.78 ± 0.33 (0.20-2.00) and eGFR <20 ml/min was 9 (12.9%), mean was 34.38 ± 16.93 (11.00-112.00). This was similar with study of Girish et al. and Gupta et al. and others where both serum creatinine and blood urea value was highly significant (P<0.05), these observation support my study.[9]

The kidneys of neonates are particularly vulnerable to hypoperfusion because of their physiologic characteristics like high renal vascular resistance, high plasma rennin activity, low glomerular filtration rate, decreased intra cortical perfusion and decreased reabsorption of sodium in the proximal tubules causes raised urea and creatinine level. [23,24]

In the present study, asphyxiated neonates had lower levels of serum Na that was 17(24.3%) & hyperkalemia were present in 15(21.4%) cases. Similar study conducted by Gupta et al.[9]

Neonatal tubular function is immature at birth and hence the capacity of sodium reabsorption is limited and if the load of sodium reaching the distal convoluted tubule increases significantly, reabsorption does not occur proportionately and the excess sodium load is excreted in urine. Occurrence of SIADH secondary to perinatal asphyxia and partial resistance to aldosterone are the other factors contributing to hyponatremia. Furthermore, hyponatremia may lead to contraction of intravascular volume resulting in worsening of the renal function.[12,24,25]

Different studies correlated renal functional status using pRIFLE criteria with renal biomarkers (uCysC and uIL). As these biomarkers are not widely available and costly, this study correlated renal impairment by using pRIFLE criteria and AKIN criteria in asphyxiated neonates, so that renal impairment can be predicted easily and early by these criteria.[11]

In previous studies there was no such type of categorization and all were considered as renal failure, hence percentage of renal failure was more in previous study. The percentages of ARF varies in different studies .In most of the studies the percentage was >40%, Gupta et al showed that 47.14%, Zulfiquar et al had found 46% of low Apgar score, Aggarwal et al showed 56%, Saha et al found 11.8%, Safaridus et al found 22.8% AKI but in my study it was 13 (18.6%) which differ from other study . As previous study did not use pRIFLE and AKIN criteria, so their percentage was high. Saha et al. used pRIFLE criteria so the result nearer to my result. According to pRIFLE criteria in my study Risk was more 77% and in AKIN criteria stage 1 was more.[22,26,27]

Conclusion

Renal impairment was found in 18.5% of term asphyxiated neonates according to pRIFLE and AKIN criteria and Biochemical parameters showed no significant changes between different stages of HIE.

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