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TO DETERMINATE THE DEGREE OR SEVERITY OF RENAL IMPAIRMENT ACCORDING TO HIE STAGES IN PNA PATIENTS

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Keywords: Perinatal Asphyxia, Acute Renal Injure, Hypoxic-Ischemic Encephalopathy.

Introduction: Perinatal asphyxia is a major cause of acute renal failure in neonates. So it is essential to evaluate renal function at an early stage to stabilize fluid and electrolyte balance which is of great importance to infants with hypoxic-ischemic encephalopathy. Yet, it is not quite easy to evaluate neonatal renal function accurately. **Objective:** To Determinate the Degree or Severity of Renal Impairment According To HIE Stages in PNA Patients. **Materials and Methods:** This cross sectional study was carried out in the department of neonatology, Chattagram Ma-O-Shishu hospital from January 2016 to June 2016. All Perinatal asphyxia patients admitted in the department of neonatology, Chattagram Maa-Shishu O General Hospital fulfilling the inclusion criteria were included in the study. As the study was done in a single center and due to time constrain 180 cases were enrolled in this study. After taking informed written consent from legal attended a total of 150 asphyxiated and 30 non-asphyxiated newborns were selected by purposive sampling. **Results**: During the study period, there were total 197 eligible infants. Among them 154 were case and 43 were control.

Among the cases 2 infants left against medical advice (LAMA), 1 infant died, and 1 was excluded due to lack of parental consent. Among the control 13 were excluded due to lack of consent. Finally 150 asphyxiated newborn were selected as case and 30 normal infants were included as control in the study. In this study, stage I, 50(60.2%) baby has normal RFI and 33 (39.8%) babies has abnormally high RFI. For stage II, 23 (43.4%) baby has normal RFI and 30 (56.6%) baby has abnormally high RFI and for stage III, only 5 (35.7%) baby has normal RFI and 9 (64.3%) baby has abnormally high RFI. There P value is 0.070, which is statistically not significant. The study also shows Mean ± SD of RFI value in stage I is 2.76 ± 0.62, for Stage II is 3.17 ± 0.67 and for stage III, is 3.17 ± 0.28 and "p" value 0.001 which is statistically highly significant. **Conclusion:** In conclusion, AKI represent a significant problem among asphyxiated neonates. All of the hyperechogenic kidney patients were also hyperuricemic, which supports the possible association between both features. In addition, uric acid itself might be the causative factor for failure in addition to hypoxic and ischemic insult. We recommend kidney functions, and abdominal ultrasonography to be done routinely in asphyxiated neonates to evaluate the possibility of acute kidney injury in them. FENa and RFI are useful parameters for assessing the renal function and urinary β2M is a good biomarker for diagnosis and prognosis of acute tubular injury in term babies with perinatal asphyxia.

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I INTRODUCTION

Perinatal asphyxia is a major cause of acute renal injury in neonates. So it is essential to evaluate renal function at an early stage to stabilize fluid and electrolyte balance which is of great importance to infants with hypoxic-ischemic encephalopathy. Yet, it is not quite easy to evaluate neonatal renal function accurately. Perinatal asphyxia is the most important preventable cause of cerebral injury in the neonatal period leading to very high neonatal mortality and morbidity in developing countries[1]. It occurs mostly during the first and second stage of labor[2] and is an eventually having far reaching consequences in the neonatal period. ARF in newborn was attributed to birth asphyxia.[3,4] 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%).[3,4,5] It results in redistribution of blood flow towards the brain, heart and adrenals and away from kidneys, skin and the gastrointestinal tract to ensure adequate oxygen and substrate deliver to these vital organs.[8,9] Hypoperfusion with concomitant hypercapnia and acidosis contribute to these organ damage.[10,11] As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis.[12] So, 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. Perinatal asphyxia occurs in 1% to 1.5% of live births in developed countries.[2] In developing countries, the incidence is greater. According to WHO, globally between four to nine million newborns suffer from perinatal asphyxia each year. Of those, an estimated 1.2 million die

(29% of all neonatal deaths) and almost the same number develop severe consequences.[13] In rural Bangladesh neonatal mortality due to perinatal asphyxia is 45%.[14] Annual reports of Dhaka Medical College Hospital from 2001 through 2007 showed incidence of birth asphyxia to be from 29% to 36% and mortality among them were around 25%.[15,16] In Dhaka Shishu Hospital 68.8% of total neonatal admission is perinatal asphyxia,[17] with a high mortality rate (44%). And in Comilla Medical College Hospital 34.17% of total neonatal admission is perinatal asphyxia with also a high mortality rate (44.5%).[18] It is a major cause of acute renal failure in newborn, 43% to 47% of asphyxiated neonates develop ARF,[18,19] and 40% to 61 % of This research has showed renal function status in patients with perinatal asphyxia. So early address to the renal status of asphyxiated babies may help in better management and outcome. The health care providers will also find a new protocol of investigation for diagnosis of renal function impairment. A United Nations Children's Fund (UNICEF) report published on Tuesday said 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 timeframe[11]. About two third of this high mortality in Bangladesh is due to high perinatal mortality. And perinatal asphyxia constitutes a large portion of perinatal mortality. It is also a leading cause of admission to neonatal care services but in our country, previously no sufficient data is available on incidence of acute renal failure in neonates with perinatal asphyxia and on relationship between low Apgar score[12] and or the hypoxic ischemic encephalopathy grading and development of acute renal failure.

II MATERIALS AND METHODS

This cross sectional study was carried out in the department of neonatology, Chattogram Ma-O-Shishu hospital from January 2016 to June 2016. All Perinatal asphyxia patients admitted in the department of neonatology, Chattogram Maa-Shishu O General Hospital fulfilling the inclusion criteria were included in the study. As the study was done in a single center and due to time constrain 180 cases were enrolled in this study. Detailed history was taken; careful physical examination was done and recorded in a structured questionnaire. Two milliliter of venous blood was collected for serum creatinine and serum Electrolyte, from study population within 72 hours to 96 hours of age. Three milliliter urine was also collected from a prefixed sterile plastic bag for Urinary electrolytes and Urinary creatinine. All these investigations were done in the department of Biochemistry laboratory, Chattagram Ma-O-Shishu hospital. Renal status was assessed by doing 1) Serum creatinine, 2) Serum Electrolyte, 3) Urinary electrolytes, 4) Urinary creatinine. When reports were available Renal failure index (RFI) were calculated. All data were preserved in the individual structured data collection form.

Data Processing and Statistical Analyses:

Data were collected and complied in a pre-tested questionnaire and analyzed by using IBM-SPSS version 20.0 for Windows (SPSS Inc. Chicago, USA) statistical software employing appropriate statistical tests like unpaired Student's "t" test, ANOVA test, mean, SD, 95% Confidence limit, Standard error and their "P" values were obtained to see the statistical significance. P value < 0.05 was considered as significant. Data was analyzed by using the software SPSS 20.0

Assessment of renal function:

Perinatal asphyxia is a major cause of acute renal failure in neonates. So it is essential to evaluate renal function at an early stage to stabilize fluid and electrolyte balance which is of great importance to infants with hypoxic-ischemic encephalopathy. Yet, it is not quite easy to evaluate neonatal renal function accurately. First of all, 7% of healthy neonates may urinate as late as the second day

of life and non-oliguric ARF is not uncommon during neonatal period.[20]

Secondly, serum BUN and creatinine levels determined during the first 24 hours of life reflect the maternal levels not those of the neonate and also increased levels of serum bilirubin and pyruvic acid in sick neonates may cause deviation in colorimetric assessment of serum creatinine level. Lastly, fractional sodium excretion (FeNa) which is an important parameter to differentiate prerenal and renal ARF should be cautiously interpreted in premature, and in neonates receiving diuretics, aminophylline and intravenous fluid with high sodium content.[21]

Renal proximal tubular cells are rich in N-acetyl-β-D glucosaminidase (NAG) which is one of lysosomalglucosidases. It has been shown that an injury to proximal tubular cells for whatever reason causes high urinary concentrations of this enzyme (enzymuria) and measurement of several tubular markers (retinol binding protein, β-2-microglobulin, myoglobinuria etc.) were found useful in diagnosis and follow-up of renal failure.[20] So, plasma creatinine concentration is of limited value in assessing renal function in the first week of life. But as we are in resource limited country, we can assess the change in blood urea and plasma creatinine concentration over a period of days in the first week of life that can give us a rough, qualitative idea of GFR. Clinical significant renal dysfunction may be evaluated by the following criterias.[22]

1. Presence of oliguria: urinary output < 1 ml/kg/hr
2. Blood urea > 40 mg/ dl
3. Serum Creatinine > 1 mg/ dl

Oliguric renal failure carried a poorer prognosis than non-oliguric renal failure ($P<0.05$). ARF perhaps does not increase mortality in already asphyxiated patients because asphyxia itself is a profound insult to the neonate and ARF additionally does not increase the stress on asphyxiated patient. As far as renal involvement in perinatal asphyxia as a system per se in considered it is second commonest organ system 42% after CNS involvement 72% to be affected in perinatal asphyxia. While renal system was the major system involved clinically i.e. oliguria 40%, raised β2M concentrations in urine 57%, elevated serum creatinine 11% followed by CNS involvement 37%.[22]

Outcome in Perinatal Asphyxia: Perinatal hypoxic-ischemic injury continues to be a major cause of neonatal death or later neurodevelopmental sequelae. The overall mortality rate is 10% to 30%. The frequency of neurodevelopmental sequel in surviving infants is approximately 15% to 45%.[2] Specific outcomes depend on severity of encephalopathy, the presence of other organ involvement. It can be ascertained using Sarnat clinical stages of Hypoxic-ischemic encephalopathy.[2]

1. Stage 1 HIE: 98% to 100% of infants have a normal outcome, <1% mortality.
2. Stage 2 HIE: 20% to 37% die or have abnormal outcomes.
3. Stage 3 HIE: 50% to 89% die and all survivors have major neurodevelopmental impairment.

III RESULTS

During the study period, there were total 197 eligible infants. Among them 154 were case and 43 were control. Among the cases 2 infants left against medical advice (LAMA), 1 infant died, and 1 was excluded due to lack of parental consent. Among the control 13 were excluded due to lack of consent. Finally 150 asphyxiated new-born were selected as case and 30 normal infants were included as control in the study. In this study, stage I, 50(60.2%) baby has normal RFI and 33 (39.8%) **babies** has abnormally high RFI. For stage II, 23 (43.4%) baby has normal RFI and 30 (56.6%) baby has abnormally high RFI and for stage III, only 5 (35.7%) baby has normal RFI and 9 (64.3%) baby has abnormally high RFI. There P value is 0.070, which is statistically not significant. The study

also shows Mean ± SD of RFI value in stage I is 2.76 ± 0.62, for Stage II is 3.17 ± 0.67 and for stage III, is 3.17 ± 0.28 and "p" value 0.001 which is statistically highly significant. The high values of the RFI signify that this AKI is intrinsic in nature.

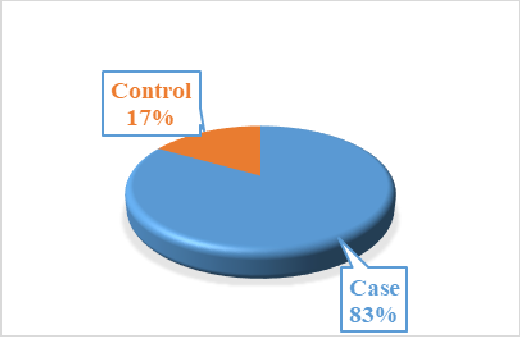

Fig.-1: Distribution of the study Groups.

Table-1: Distribution of the study subjects (n = 180)

Study Groups	Frequency	Percentage (%)
Case	150	83.3
Control	30	16.7
Total	180	100.0
* *PNA = Perinatal Asphyxia*		
Cases	*Frequency*	*Percentage (%)*
PNA with HIE stage I	83	55.4
PNA with HIE stage II	53	35.3
PNA with HIE stage III	14	9.3
Total	150	100.0
*PNA = Perinatal Asphyxia		

Table -2: Distribution of the socio-demographic variables among the study subjects (n = 180)

Socio-demographic Variables		**Study Groups**		**Total(n = 180)**
		(n = 150)	**(n = 30)**	
Sex	Male	80 (53.3)	14 (46.7)	94 (52.2)
	Female	70 (46.7)	16 (53.3)	86 (47.8)
Residence	Rural	94 (62.7)	13 (43.3)	107 (59.4)
	Urban	56 (37.3)	17 (56.7)	73 (40.6)
Place of Delivery	Home Hospital	87 (58) 63 (42)	6 (20) 24 (80)	93(51.7) 87 (48.3)
Mode of Delivery	NVD LUCS	98 (65.3) 52 (34.7)	20 (66.7) 10 (33.3)	118 (65.6) 62 (34.5)
• Figures within parentheses indicate percentages				

Table-3: Statistics of *RFI* among the study subjects (n =180)

RFI	N	Mean	±SD	Median	Range	P Value*
Case (Newborn with PNA)	150	2.94	0.64	2.98	1.32 – 5.39	P < 0.001
Control	30	1.49	0.54	1.42	0.74 – 2.53	Highly Significant
	180	2.70	0.83	2.90	0.74 – 5.39	* t-test
PNA = Perinatal Asphyxia; RFI = Renal Failure Index						

This table shows the mean value of Renal Failure Index (RFI) in case is 2.94 ±0.64 and in control is 1.49±0.54 which is statistically significant (P value is <0.001).

Table-4: Distribution of RFI by stages (with t-test and ANOVA significance)

RFI		Stages		p value*
	Stage I	Stage II	Stage III	
Normal	50 (60.2)	23 (43.4)	5 (35.7)	0.070
Abnormal	33 (39.8)	30 (56.6)	9 (64.3)	
Total	83 (100.0)	53 (100.0)	14 (100.0)	

Figure within parentheses indicates in percentage.

Table 4: Stage wise prevalence of HIE

RFI	N	Mean	SD	Median	Range	p-value
PNA with HIE stage I	83	2.76	0.62	2.90	1.32 – 4.85	P < 0.001 *Highly Significant*
PNA with HIE stage II	53	3.17	0.67	3.06	1.61 – 5.39	
PNA with HIE stage III	14	3.17	0.27	3.22	2.72 – 3.62	
Total	150	2.94	0.64	2.98	1.32-5.39	*ANOVA

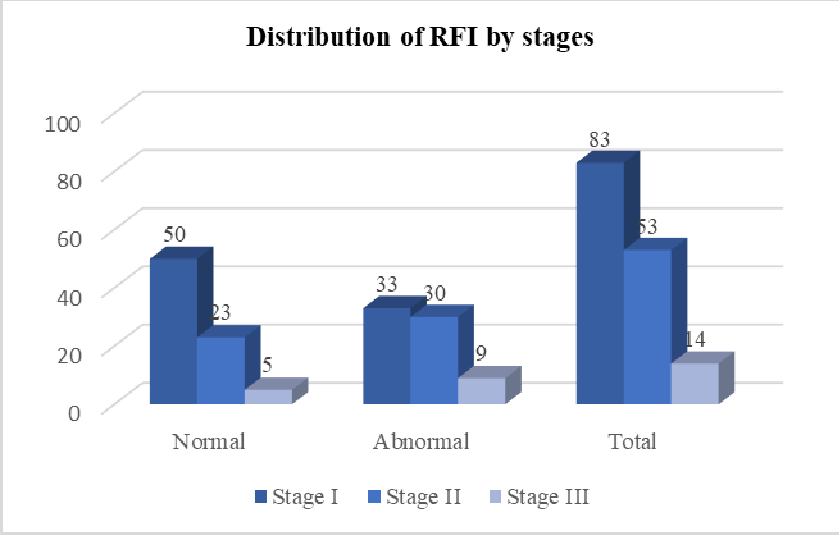

Fig.-2: Distribution of RFI by stages.

In this table it is shown that perinatal asphyxia is more common in male sex than female sex (53% Vs 47%), People of rural area than urban (62.7% Vs 37.3%), Home delivery than hospital delivery (58% Vs 42%) and NVD than LUCS (65.3 Vs 34.7). This table shows normal and abnormal values of RFI in stage I, stage II and stage III are significant statistically and their mean values are also statistically significant.

IV DISCUSSION

Perinatal asphyxia is one of the important causes of neonatal morbidity and mortality in Bangladesh.[14] The kidneys are the commonest organs to be involved in perinatal asphyxia and it is very sensitive to ischemic damage.[4] So, the renal function assessment in perinatal asphyxia is essential for accurate management of metabolic derangement particularly fluid, electrolytes and acid base imbalance resulting from renal function impairment. 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.[23] Traditionally, assessment of perinatal asphyxia has relied on a combination of clinical observations such as Apgar score and measurement of serum creatinine level. There was weakness in such methods because Apgar score may be influenced by metabolic and chromosomal disorders other than perinatal asphyxia. So, determination of more sensitive and specific markers of renal tubular dysfunction of renal injury in perinatal asphyxia is essential.[24] In this study 180 neonates with perinatal asphyxia of different stages were enrolled, among them 150 patients were cases and 30 patients were control. Our study revealed a 71.4 % mortality rate (p=0.001) and an average mortality at 4 days. There was 24-fold increase risk of death in AKI, p=0.001 with 95% CI (3.7–157). The high mortality rate and wide confidence interval could have been contributed to by the small sample size. AKI is not normally a direct cause of death.[15] In my study among 150 cases 55% were HIE stage I, 35% were HIE stage II and 9% were HIE stage III. In this study, stage I, 50(60.2%) baby has normal RFI and 33 (39.8%) abies has abnormally high RFI. For stage II, 23 (43.4%) baby has normal RFI and 30 (56.6%) baby has abnormally high RFI and for stage III, only 5 (35.7%) baby has normal RFI and 9 (64.3%) baby has abnormally high RFI. There P value is 0.070, which is statistically not significant. The study also shows Mean ± SD of RFI value in stage I is 2.76 ± 0.62, for Stage II is 3.17 ± 0.67 and for stage III, is 3.17 ± 0.28 and "p" value 0.001 which is statistically highly significant. The high values of the FeNa and RFI signify that this AKI is intrinsic in nature. Among the cases, on the basis of clinical status, 83 (55%) neonates were assigned as HIE stage I, 53 (35%) neonates were assigned as HIE stage II and 14 (9%) neonates were assigned as HIE III. Neonates who develop nonoliguric ARF have better survival rates than those who suffer from oliguric ARF. The overall mortality rate in oligoanuric neonatal ARF ranges from 25% to 78%. Recovery from ARF in the neonate is unrelated to nonrenal factors such as age at diagnosis, birth weight, Apgar scores, or requirement for ventilator support. Blood urea nitrogen, peak serum creatinine, and urine flow rate have been reported to be inadequate discriminators of renal outcome.[25]

CONCLUSION

In conclusion, ARF represent a significant problem among asphyxiated neonates. All of the hyperechogenic kidney patients were also hyperuricemic, which supports the possible association between both features. In addition, uric acid itself might be the causative factor for failure in addition to hypoxic and ischemic insult. We recommend kidney functions, and abdominal ultrasonography to be done routinely in asphyxiated neonates to evaluate the possibility of acute kidney injury in them.

FeNa and RFI are useful parameters for assessing the renal function and urinary β2M is a good biomarker for diagnosis and prognosis of acute tubular injury in term babies with perinatal asphyxia.

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