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Original Article

Paediatrics Section

Renal Functions in Relation to Severity of Perinatal Asphyxia in Term Neonates

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ABSTRACT

Introduction: Kidney is one of the most important organs commonly involved in the multiple organ dysfunction caused by perinatal asphyxia. Monitoring the serum urea, creatinine and urine output helps in early assessment of severity of perinatal asphyxia and, thus improving the outcome.

Aim: To study renal functions in perinatal asphyxia and various stages of Hypoxic-Ischemic Encephalopathy (HIE) in term neonates.

Materials and Methods: This observational study included 118 full-term perinatally asphyxiated neonates admitted in Neonatal Intensive Care Unit (NICU) of Uttar Pradesh University of Medical Sciences, Saifai, Etawah. Serum urea, creatinine and urine output were assessed on 1st, 3rd and 10th day of admission. A total of 48 newborns with normal Renal Function Test (RFT) and urine output were kept in Group A, while 70 newborn with abnormal RFT and urine output were kept in group B. To compare RFT in various HIE stages of perinatal asphyxia, neonates were graded by the Levene staging system and divided in mild HIE (stage I), moderate HIE (stage II) and severe HIE (stage III). A total of 52 neonates who did not fulfill criteria of any stage of Levene were diagnosed as asphyxia without HIE and were excluded from comparison.

Results: Significant differences (p-value <0.05) in serum urea, creatinine and urine output were found between Group A and B on postnatal day 1, 3 and 10. Total 66 neonates were diagnosed to have hypoxic ischemic encephalopathy with various grades (Stage I-15, Stage II-32 and Stage III-19). Rest 52 neonates were suffering from perinatal asphyxia but did not come in any category of HIE. On day 1, there was an increasing trend in concentration of both serum urea and serum creatinine as HIE staging progressed from HIE I to HIE III. On Day 3, serum urea and creatinine were found to be significantly higher in HIE III compare to HIE II. On day 10, serum urea and creatinine were significantly higher in HIE III as compared to HIE I and II. In all three days, urine output decreased as HIE stages progressed to I to III.

Conclusion: Renal dysfunction correlates well with increasing severity of asphyxia in terms of HIE staging and it can be used as marker to assess the severity of perinatal asphyxia.

Keywords: Hypoxic ischemic encephalopathy, Renal dysfunction, Serum creatinine, Serum urea

INTRODUCTION

Perinatal asphyxia is the condition resulting from lack of oxygen (hypoxia) or lack of perfusion (ischemia) to fetus or newborn to cause various organ dysfunction of sufficient magnitude and duration [1]. The burden of birth asphyxia in neonates is so high that every hour 104 children die due to the disease, and the condition is alarming in India as between 250,000 to 350,000 infant deaths are reported annually, mostly within the first three days of life [2]. The birth asphyxia affect almost every organ of the body and the most frequently affected organs are kidneys (50%), central nervous system (28%), cardiovascular (25%) and pulmonary system (23%) [3]. In absence of perinatal record, it is very difficult to diagnose and grade the asphyxia after delivery [4,5]. There is a need to identify neonates with asphyxia who will be at risk for hypoxic ischemic encephalopathy and multi-organ dysfunction. Kidney is one of the most important organs commonly involved in the multiple organ dysfunction caused by perinatal asphyxia. Renal injury in birth asphyxia is a potential consequence of an adaptive mechanism [6]. Amongst the recognised complications, Acute Renal Failure (ARF) is the most common and carries a poor prognosis and even 40% of survivors may develop permanent renal damage [7]. The novelty of our study is that we had compared renal dysfunction in different stages of HIE (Levene staging) and also assessed the renal function on postnatal day 1, 3 and 10. Literature regarding comparison in HIE staging is not much and very few studies have shown the renal derangement as the disease progresses [8,9]. We should keep a high index of suspicion of

renal dysfunction in asphyxiated neonates. By this way, we can recognise early derangements of renal function in asphyxiated neonates according to their HIE stage which can be helpful in management of perinatal asphyxiated neonates, so we can reduce the mortality and morbidity in perinatally asphyxiated term neonates. Hence, the present study was conducted with an aim to study renal functions in perinatal asphyxia and various stages of HIE in term neonates.

MATERIALS AND METHODS

This prospective observational study was conducted in the NICU of University of Medical Sciences, Saifai, Etawah (UPUMS), Saifai, Etawah, India, for a period of one year and six months from January 2017 to June 2018. All the patients fulfilling the inclusion criteria within this time frame of the study were considered eligible. The study was approved by the Ethical Committee (EC No. 2017/155) of the UPUMS, Saifai, Etawah. Parents gave their written, informed consent for the enrolment of their children in the study. All full-term asphyxiated neonates (n=146), determined by any of the following criteria, i.e., Failure to initiate and sustain breathing at birth (WHO criteria) or Apgar score <7 at 1 minute of age {National Neonatal Perinatal Database (NNPD) criteria}, born in the institute and admitted in NICU of the department of Pediatrics of UPUMS, Saifai, Etawah during the study period were enrolled [10]. Neonates whose parents were not willing to give consent for participation, preterm (<37 weeks of gestation), out born, congenital malformations and congenital infections, confirmed or suspected clinical meningitis, nonvigorous meconium stained liquor, maternal USG during pregnancy showing any structural abnormality of fetal kidney, surgical conditions like necrotising enterocolitis and tracheo-esophageal fistula, structural disease of kidney confirmed by ultrasonography, neonates with sepsis (positive sepsis screen and or positive blood culture) and neonates with primary disease of kidney were excluded from the study. Neonates with deranged baseline RFT as per age reference values in presence of normal maternal RFT were assumed to have primary disease of kidney. RFT was assessed from patient's serum, on the Randox Imola auto-analyser available in the central biochemistry lab of the institute. The reference values of serum urea and creatinine for term neonates were taken as 3-12 mg/dL and 0.3-1.0 mg/dL, respectively [11].

A total of 28 neonates were excluded and total 118 neonates were analysed for final results. Complete antenatal, perinatal and postnatal history was recorded in a predefined study proforma. Full medical history especially the history of anaesthesia during caesarean section and drug intake by mother or infant were recorded. Complete physical & systemic examination including detailed neurological examination was done at the time of admission. Gestational age, birth weight, findings on physical examination and systemic examination were recorded on a predesigned pretested study proforma. Gestational age of newborn was assessed by the New Ballard score [12]. All asphyxiated neonates were also graded into HIE stages by the Levene staging system for HIE. The classification system modified by Levene has three stages-mild HIE (I), moderate HIE (II), severe HIE (III) based on clinical observation [13]. In HIE stage I, no seizures are experienced and the neonate is irritable, tone is decreased & sucking is poor. In HIE stage II, neonate is lethargic, marked hypotonic, unable to suck & seizures are usually seen within 12 hours after birth. In HIE stage III, neonate is comatose, severely hypotonic, unable to maintain spontaneous respiration & seizures are prolonged. Maternal renal functions (serum urea & serum creatinine) prior to delivery were also measured.

After admission in NICU, baseline venous blood samples were withdrawn under aseptic conditions. Venous Blood samples were collected in appropriate vials for routine base line investigation like Complete blood count, Random blood sugar, C-reactive proteins, Serum electrolytes, blood culture and RFT at the time of NICU admission (Day 1). All blood samples were sent to the central laboratory of the hospital within 30 minutes of collection for estimation of biochemical parameter. RFT were again repeated on day 3 & day 10. USG abdomen of all enrolled neonate was done to rule out the suspected primary disease of kidney, i.e., any structural abnormality of fetal kidney. Kidney size, echo texture and corticomedullary differentiation were noted on ultrasonography. Urine output monitoring was done daily since admission to 10th day of life. Oliguric renal failure was defined as urine output <1 mL/kg/hr for past 12 hours in a baby more than 24 hours of age [14].

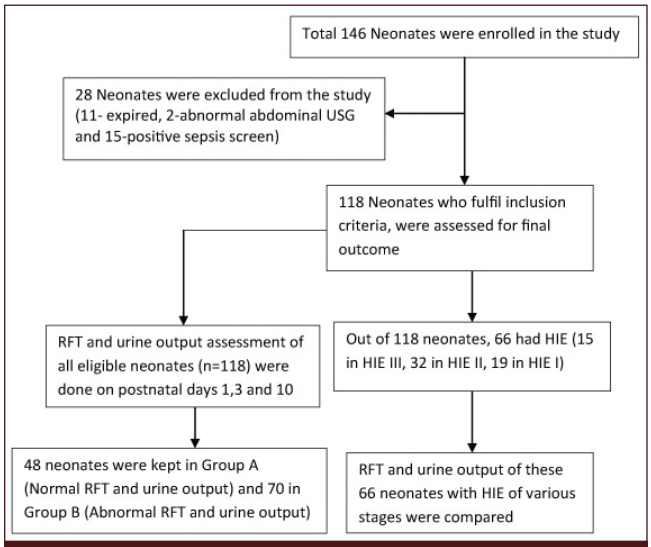
Asphyxiated babies with normal kidney functions (n=48) were grouped as A and asphyxiated babies with abnormal kidney functions (n=70) were grouped as B [Table/Fig-1]. Asphyxiated newborn (with our without deranged renal function) were managed conservatively as per the standard NICU protocols.

STATISTICAL ANALYSIS

All the data was collected, compiled, analysed using SPSS (Statistical Package for Social Sciences) Version 22.0 statistical analysis software and inter-operated statistically through relevant statistical methods like student's test (unpaired t-test) to compare renal function in various HIE stages.

RESULTS

Out of 118 newborns suffering from perinatal asphyxia, 85 (72%) were males and 33 (28%) were female babies. A total of 38 (32%) newborns had severe birth asphyxia (Apgar score 0-3 at 1 minute) and 80 (68%) had moderate birth asphyxia (Apgar score 4-6 at 1 minute). On day 1, average serum urea and serum creatinine were 20.07±14.50 mg/dL and 0.85±0.49 mg/dL, respectively and urine output was found to be 1.24±0.40



[Table/Fig-1]: Study flow chart.

mL/kg/hr. Out of total 118 asphyxiated newborns, 48 (40.67%) had normal renal function (group A) and 70 (59.32%) had abnormal renal function (group B). In group B, the mean value of serum urea and creatinine were significantly higher and urine output values were significantly lower in comparison of group A [Table/Fig-2]. On day 3, mean serum urea was 24.41±14.11 mg/dL, mean serum creatinine was 0.92±0.52 mg/dL and urine output was 1.25±0.38 mL/kg/hr. Out of total 118 asphyxiated newborns, 47 (39.83%) had normal RFT (group A) and 71 (60.16%) had abnormal RFT (group B). In group B, mean serum urea and creatinine were significantly higher and urine output values were significantly lower in comparison of group A. On day 10, mean serum urea, creatinine and urine output were 10.29±2.12 mg/dL, 0.32±0.19 mg/dL and 1.40±0.20 mL/kg/hr, respectively. Total 114 (96.61%) newborns had normal kidney functions while 4 (3.38%) had abnormal kidney functions. On comparison between group A and group B, results were statistically significant for serum urea, serum creatinine and urine output on Day 10 [Table/Fig-2].

Total 66 (55.93%) neonates were diagnosed to have HIE with various grades (Stage I-15, Stage II-32 and Stage III-19) according to Levene staging as described earlier, rest 52(44.06%) neonates suffered from perinatal asphyxia but did not come in any category of HIE. On Day 1, there was an increasing trend in concentration of both serum urea and serum creatinine as HIE staging of neonates progressed from HIE I to HIE stage III. As the HIE stage increased, the urine output decreased. On Day 3 serum urea levels were statistically insignificant when compared to HIE I-II and HIE I-III stages. Serum creatinine levels were statistically significant when compared to various HIE stages.

On day 3 result of urine output were comparable & statistically significant between different HIE stages. On day 10 comparison of various parameters of RFT in HIE I vs HIE II neonates were statistically insignificant while it was statistically significant on comparison in between HIE I vs HIE III and HIE II vs HIE III [Table/Fig-3].

DISCUSSION

Neonatal birth asphyxia is known to cause multiple organ dysfunctions in one-way or other. In the present study biochemical parameters suggestive of renal dysfunction, urine output and hemodynamic status of asphyxiated neonates were monitored and found significant differences in comparison with different HIE stages. It is very important to know that significant Acute Kidney Injury (AKI) can also occur in neonates who are non oliguric. In the present study, 80% of neonates with abnormal RFT were nonoliguric which was comparable to the results seen in study conducted by Gupta BD et al., where nonoliguric renal failure was found to be 78% [6]. Earlier studies by Aggarwal A et al., found 56% of asphyxiated neonates had abnormal renal function which was almost similar to our study in which we found 59.32% had abnormal renal functions [15]. In a study Pammi V et al., also found that 72% of neonates suffering from asphyxia had either oliguric or nonoliguric renal failure [16].

RFT	Days	Group A	Group B	Total	p-value
Serum urea (mg/dL)	Day 1	6.57±2.23 (n=48)	29.34±11.90 (n=70)	20.07±14.50 (n=118)	<0.001
	Day 3	10.27±1.65 (n=47)	33.77±10.39 (n=71)	24.41±14.11 (n=118)	<0.001
	Day 10	10.02±1.20 (n=114)	17.82±6.61 (n=4)	10.29±2.12 (n=118)	<0.001
Serum creatinine (mg/dL)	Day 1	0.33±0.08 (n=48)	1.21±0.29 (n=70)	0.85±0.49 (n=118)	<0.001
	Day 3	0.37±0.09 (n=47)	1.28±0.34 (n=71)	0.92±0.52 (n =118)	<0.001
	Day 10	0.29±0.11 (n=114)	1.17±0.13 (n=4)	0.32±0.19 (n=118)	<0.001
Urine output (mL/kg/hr)	Day 1	1.37±0.18 (n=48)	1.15±0.48 (n=70)	1.24±0.40 (n=118)	0.005
	Day 3	1.38±0.21 (n=47)	1.17±0.44 (n=71)	1.25±0.38 (n=118)	0.002
	Day 10	1.41±0.20 (n=114)	1.17±0.17 (n=4)	1.40±0.20 (n=118)	0.022

[Table/Fig-2]: Comparison of mean serum urea, creatinine and urine output between group A (Normal RFT and Urine output) and group B (Abnormal RFT and Urine output) on postnatal day 1, 3 and 10.
Unpaired t-test was used

RFT	Days	HIE III (n=19)	HIE II (n=32)	HIE I (n=15)	p-value (I vs II)	p-value (I vs III)	p-value (II vs III)
Serum urea (mg/dL)	Day 1	42.97±9.10	28.85±8.90	21.08±9.54	0.003	<0.001	<0.001
	Day 3	40.63±10.47	31.42±8.98	33.98±11.04	0.714	0.103	0.003
	Day 10	12.72±4.44	9.73±1.21	9.75±1.15	0.958	0.008	0.001
Serum creatinine (mg/dL)	Day 1	1.36±0.22	1.24±0.32	1.02±0.20	0.031	0.002	0.481
	Day 3	1.54±0.27	1.30±0.35	1.07±0.20	0.030	0.001	0.048
	Day 10	0.59±0.37	0.27±0.13	0.25±0.11	0.506	0.001	<0.001
Urine Output (mL/kg/hr)	Day 1	0.90±0.18	1.38±0.30	1.37±0.16	0.920	<0.001	<0.001
	Day 3	0.92±0.24	1.26±0.25	1.39±0.24	<0.001	<0.001	<0.001
	Day 10	1.24±0.20	1.35±0.16	1.43±0.11	0.201	0.016	0.022

[Table/Fig-3]: Renal Function Test (RFT) and Urine Output on postnatal Day 1, 3, 10 and there comparison in different HIE groups. Unpaired t-test was used

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. Jayshree G et al., noted that there was significantly higher incidence of ARF in stage 2 and 3 as compared to stage 0 and 1 [17]. Kidney functions assessed by Jayaswal A et al., in 40 neonates of different HIE stages on day 3 and 5 of age showed significant difference. Similar to our finding in their study as the HIE stage increased biochemical derangement increased [18]. In a study by Medani SA et al., found AKI in 54.1% of neonates diagnosed as HIE. Contemporary to other studies most of them belonged to stage II (63%) of HIE, instead of stage III. This can be due to the variation in age group according to days of life in their study and higher mortality in stage III [19]. Like most of the studies Reddy S et al., also found ARF in 100% of stage III, 81.2% of stage II and least 7.1% of neonates suffering from stage I [20].

Strength of this study were good sample size, less allowable error for sample size calculation & well defined age wise cut-off levels used to define renal dysfunction for enrolling study population. We had used postnatal day wise cut-off levels of various parameters of RFT for labeling abnormal RFT. In this study we had taken neonates with normal maternal serum urea & serum creatinine (prior of delivery) to remove maternal effects on RFT. Exclusion of all neonates with sepsis confirmed by positive sepsis screen or blood culture to remove effects of sepsis on RFT. We had also excluded neonates with an abnormal sonographic appearance of kidney to eliminate the primary disease of kidney.

With the help of this study and other studies on renal dysfunction due to asphyxial effects, many things have been increasingly recognised. But still there are many unanswered questions on this topic. First of all, there is a need to develop a consensus for defining asphyxiated neonates enrolled as study population. Although renal dysfunction in the present study showed a good correlation with hypoxic ischemic injury, a large multi-centric trial is required to confirm present study observations. This study highlighted the effects of asphyxia on renal functions as a multisystem insult. Still, the long term effects of asphyxia on renal functions remain unanswered which may be an interest for further studies. Effect of medications used during the management of asphyxia and its complications on renal dysfunction and longer outcome still have to be answered which might need some further studies.

Limitation(s)

Limitation of the study was that we had taken WHO & NNPD criteria for enrolling study population and we did not include all criteria of American Academy of Paediatrics for labeling them as perinatal asphyxia (we did not take umbilical cord blood sample to see metabolic or mixed academia). Because of infrequent follow-up, long term neurodevelopmental outcomes were also not assessed to see the correlation between severity of renal dysfunction and neurodevelopmental outcome.

CONCLUSION(S)

Renal dysfunction is a common finding present in patients of perinatal asphyxia. Renal derangement increases with severity of disease. HIE stage III has more renal function derangement compared to stage I and II. So, renal function derangement in perinatal asphyxia can be used as an early predictor of severity of disease and helpful for early management and vigorous monitoring of neonates.

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