Acute kidney injury in asphyxiated neonates and its correlation to hypoxic ischemic encephalopathy staging

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ABSTRACT

Background: Acute kidney injury (AKI) is a common consequence of perinatal asphyxia, occurring in up to 56% of these neonates. It is important to recognize AKI in asphyxiated neonates to facilitate administration of appropriate fluids and electrolytes to improve their outcome. **Objectives:** To determine the incidence of AKI in asphyxiated neonates and its correlation with severity of hypoxic-ischemic encephalopathy (HIE). **Methods:** 135 term neonates were enrolled - 90 asphyxiated and 45 healthy neonates. AKI was diagnosed when serum creatinine was >1.5 mg/dl regardless of the rate of urine output (UOP). Neonates with AKI were managed as per standard protocol. **Results:** Of the 90 asphyxiated neonates, 68 (75.6%) had AKI including 58 (85.3%) neonates with pre-renal AKI and 10 (14.7%) with intrinsic AKI. Out of the 68 AKI, 22 (32.36%) had oliguric AKI and 46 (67.64%) had non-oliguric AKI. Levels of blood urea and serum creatinine were significantly higher in asphyxiated neonates as compared to healthy controls (p<0.001). There was no significant difference in UOP in control and study groups. Sonographic abnormalities were seen mostly in oliguric babies and indicated bad prognosis. Mortality was higher in babies with oliguric AKI. **Conclusions:** Perinatal asphyxia is an important cause of neonatal AKI. The majority had non-oliguric AKI and responded well to fluid challenge. Abnormalities in the renal function correlate well with the severity of HIE. Intrinsic AKI, oliguria, hyponatremia, reduced creatinine clearance, and abnormal sonographic scan suggest bad prognosis in neonatal AKI secondary to perinatal asphyxia.

Key words: *Acute kidney injury, Hypoxic ischemic encephalopathy, Intrinsic renal acute kidney injury, Prerenal acute kidney injury*

The World Health Organization has defined birth asphyxia as "failure to initiate and sustain breathing at birth and as an Apgar score of <7 at 1 min of life" [1,2]. The essential criteria for diagnosing perinatal asphyxia as outlined by the American College of Obstetrics and Gynaecology and American Academy of Paediatrics are [3,4] prolonged metabolic or mixed acidemia (pH <7.0 on cord arterial blood sample), persistence of an Apgar score of <3 for 5 min or longer, clinical neurologic manifestation as seizures, hypotonia, coma or hypoxic-ischemic encephalopathy (HIE) in the immediate neonatal period, or evidence of multi-organ system dysfunction in the immediate neonatal period.

Asphyxia remains a common problem in the neonatal nursery and is a significant cause of morbidity and mortality in the term and preterm neonate. It causes redistribution of cardiac output to maintain cerebral, cardiac, and adrenal perfusion while potentially compromising renal, gastrointestinal, and skin perfusion. It is, therefore, not surprising that acute kidney injury (AKI) is quite common in the asphyxiated neonate. Hypoxia and ischemia can cause damage to the almost every tissue and organ of the body and various target organs involved have been reported to be

kidneys in 50% cases [5] followed by CNS in 28%, CVS in 25%, and lungs in 23% cases [6-8].

As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 h of a hypoxic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis. The incidence of AKI has ranged from 0.4% of live births to 3.5% of hospital admission to 8% of admission to neonatal intensive care unit [9-11]. Criteria for defining AKI in neonates are serum creatinine ≥1.5 mg/dl, independent of day of life and regardless of the rate of urine output (UOP) [1]. Early recognition of AKI is important in babies with HIE to facilitate appropriate fluid and electrolyte management as a stable biochemical milieu is vital.

HIE is an encephalopathy resulting from hypoxic-ischemic brain injury following perinatal asphyxia. The following severe birth asphyxia, 25% infants are likely to develop syndrome of HIE [3]. Asphyxia may be suspected and HIE reasonably included in the differential diagnosis when there is prolonged (>1 h) antenatal acidosis, fetal HR <60 beats/min, Apgar score ≤3 at ≥10 min, need for positive pressure ventilation for >1 min or 1st cry delayed >5 min, seizures within 12-24 h

of birth, burst suppression or suppressed background pattern on electroencephalography (EEG), or amplitude-integrated EEG.

MATERIALS AND METHODS

This prospective cohort study was carried out in the department of pediatrics of a tertiary care teaching institute, over a period of 1-year from April 2015 to March 2016. Approval from the institutional ethics committee was obtained before staring the study. The study included 90 term neonates with gestation between 37 and 42 weeks with Apgar score of 7/<7 at 5 min after birth as cases and 45 normal term (37-42 weeks) neonates were selected as controls using stratified random sampling. Neonates with confounding factor believed to alter renal functions such as septicemia, respiratory distress syndrome, necrotizing enterocolitis, major congenital anomalies, on intravenous nephrotoxic drugs having a history of maternal drug intake, or maternal fever, gestational age <37 weeks/>42 weeks are excluded from the study.

Gestational age, birth weight, relevant perinatal history, and examination findings were recorded in predesigned pro forma. Assessment of the neurologic status included Sarnat and Sarnat staging for HIE along with an assessment of anterior fontanel, tone, seizures, pupil size, and reaction every 12 hourly. Seizures were treated energetically. All neonates were closely monitored clinically and were managed according to the standard guidelines. This monitoring aimed to detect derangements in the clinical, metabolic, and hemodynamic milieu so as to ensure prompt management. 24 h UOP was monitored by applying plastic collection bag. After obtaining written consent from the parents, between 72 h and 96 h of birth 3 ml blood was drawn under aseptic precautions and was evaluated for blood urea (Berthelot method), serum creatinine (Jaffe's test), and serum electrolytes (calorimetric method).

Criteria adopted for defining AKI in neonates was serum creatinine ≥1.5 mg/dl, independent of day of life and regardless of UOP. Those neonates who fulfilled the above criteria were diagnosed as AKI, were the first given a fluid challenge with 10 ml/kg normal saline over 20 min, and were monitored for UOP and clinical parameters. If UOP remained <1 ml/kg/h, it was then followed by diuretic (injection furosemide 1 mg/kg) [12] and if UOP still remained <1 ml/kg/h, then these neonates were diagnosed as having intrinsic renal failure and peritoneal dialysis was planned (as per the indications).

Descriptive statistical analysis has been performed in the present study. The results on continuous measurements are presented in mean ± standard deviation (Min-Max), and the results on categorical measurements are presented in number (%). A significance is assessed at 5% level of significance. Student t-test (two-tailed, independent) has been used to find out the significance of study parameters on continuous scale between two groups. Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups. A statistical software SPSS version 15.0 was used for the analysis of the data.

RESULTS

Of the 90 asphyxiated neonates, 68 (75.6%) had AKI and out of them, 58 (85.3%) had pre-renal AKI and 10 (14.7%) had intrinsic AKI. Out of the 68 AKI cases, 22 (32.36%) had oliguric and 46 (67.64%) had non-oliguric AKI as shown in Table 1. The incidence of AKI had a strong correlation with the staging of HIE. 19 (52.8%) of the neonates with HIE-I had AKI, while 40 (88.9%) of HIE-II cases had AKI and 9 out of 9 (100%) cases with HIE-III AKI (Table 2). Distribution of type of AKI shows all cases with HIE-I had pre-renal and 13 (68.4%) had non-oliguric AKI, while 39 (97.5%) cases with HIE-II had pre-renal and 28 (70%) had non-oliguric AKI. All 9 cases with HIE-III had intrinsic AKI and 5 (55.6%) had non-oliguric AKI as shown in Table 2.

The levels of blood urea and serum creatinine were significantly higher in asphyxiated neonates as compared to healthy controls (p<0.001). Sonographic abnormalities were seen mostly in the oliguric babies and indicated worse prognosis. Out of 90 cases, 58 (85.3%) improved clinically after fluid therapy (i.e., they had pre-renal failure), while 10 (14.7%) did not improve (had intrinsic renal failure). The mortality was 11.76% [8 cases], of which 5 (62.5) had non-oliguric AKI and 3 (37.5%) had oliguric AKI. All the 8 deaths occurred in neonates with intrinsic renal failure. Among them, 6 had associated morbidities and refused peritoneal dialysis, 2 underwent peritoneal dialysis but could not be improved. 2 neonates were taken against medical advice.

DISCUSSION

Perinatal asphyxia can result in multisystem organ damage in a neonate, renal system being the most common (in 50% cases followed by CNS in 28%, CVS in 25%, and lungs in 23% cases). Perinatal asphyxia is an important cause of neonatal AKI. In our study, the incidence of AKI in asphyxiated neonates was 75.56%. The majority had non-oliguric AKI and responded well to fluid challenge. Abnormalities in the renal function correlate well with the severity of HIE.

In a study by Gupta et al., the incidence of AKI in asphyxiated neonates was 47.14%. However, they studied 70 neonates and of them 32 cases had no HIE features [13]. Non-oliguric renal failure was a more common as seen in our study. Aggarwal et al. studied 25 cases and showed that incidence of AKI was 56%, which was less as compared to our study [2]. This could be due to the fact that they have excluded the neonates who died within four days, and probably these were the neonates who might have suffered severe asphyxia and might have AKI. Although, they did not mention about the distribution of

Table 1: Type of AKI in cases and controls

AKI	Total	Prerenal (%)	Intrinsic renal (%)	Oliguric (%)	Non-oliguric (%)
Cases	68	58 (85.3)	10 (14.7)	22 (32.36)	46 (67.64)
Controls	2	2 (100)	0	0 (0)	2 (100)

AKI: Acute kidney injury

Table 2: Incidence and type of AKI and its correlation among different stages of HIE

HIE staging	Total neonates	AKI (%)	Prerenal AKI (%)	Intrinsic AKI (%)	Oliguric (%)	Non-oliguric (%)
HIE 1	36	19 (52.8)	19 (100)	0 (0)	6 (31.6)	13 (68.4)
HIE 2	45	40 (88.9)	39 (97.5)	1 (2.5)	12 (30)	28 (70)
HIE 3	09	09 (100)	0 (0)	09 (100)	4 (44.4)	5 (55.6)
Total	90	68 (75.6)	58 (85.3)	10 (14.7)	22 (32.4)	46 (67.6)
p		<0.001				

AKI: Acute kidney injury, HIE: Hypoxic-ischemic encephalopathy

Table 3: Comparative studies showing the incidence of AKI among the cases

Studies	Year	AKI (%)	Oliguric AKI (%)	Non oliguric AKI (%)
Gupta et al. [13]	2005	47.14	21.21	78.78
Aggarwal et al. [2]	2005	56	42	58
Karlowicz et al. [14]	1995	61	40	60
Jayashree et al. [15]	1991	43.3	69.2	30.8
Mohan et al. [16]	2000	72	44	56
Present study	2015	75.56	32.36	67.64

AKI: Acute kidney injury

neonates according to HIE staging. Non-oliguric AKI cases were more common in their study (Table 3). Karlowicz and Adelman found 61% incidence of AKI in asphyxiated neonates and non-oliguric type was more common [14].

Jayshree et al. showed that the incidence of AKI in asphyxiated neonates was only 43.3% as compared to 75% in our study, and oliguric AKI was more common in their study [15]. This difference can be due to criteria adopted by them, i.e., neonate presenting with oliguria (UOP <1 ml/kg/h), blood urea >40 mg/dl, or serum creatinine >1 mg/dl was subjected to an intravenous fluid challenge of 20 ml/kg. After 30 min if oliguria persisted, it was followed by injection furosemide 2 mg/kg, if oliguria still persisted then the infant was diagnosed as AKI.

Mohan et al. in their study showed that the incidence of AKI was 72%, when AKI was defined as blood urea nitrogen >20 mg/dl on at least 2 blood samples and oliguria (UOP <1 ml/kg/h) [16]. Their study showed that nonoliguric was more common. In our study, the incidence of AKI in asphyxiated neonates was higher (75.56%) than in other studies as shown in Table 3 and possible causes could be all asphyxiated neonates with features of HIE in all 3 stages were studied. Second, the criteria adopted for defining AKI was serum creatinine of >2 SD above the mean value for gestational age (or >1.5 mg/dl), which no other study had used.

This helped in the management of neonates at an early stage where the neonates had pre-renal failure and responded well to the fluid challenge and had 100% recovery highlighting that the kidneys are the most susceptible organs to ischemic hypoxic injury because of redistribution of the blood flow to other vital organs. Unique vascular supply of renal medulla results in transient loss of renal concentrating capacity. More prolonged injury produces widespread tubular dysfunction and progress to intrinsic renal failure.

In our study, the most common type was nonoliguric. This can be explained as due to decreased pituitary release of vasopressin

or renal responsiveness to vasopressin and heterogeneous response of individual nephron and variable damage to the tubular epithelium results in the reduction in GFR, decreased tubular fluid flow and subsequent decrease in fractional reabsorption from tubules. However, only oliguria will not determine AKI and even neonates who are nonoliguric can have AKI which is a more common presentation in birth asphyxia and should not be missed. One should also be aware of the fact that term neonates may void for the first time at around 30 h of life. Hence, it is very essential to monitor renal parameters along with the routine use of ultrasonography of abdomen to look for renal status in asphyxiated neonates.

It is very important to differentiate between prerenal and intrinsic renal failure as in the former the damage to kidney is yet to begin whereas in the later it has already. The renal injury in most cases is prerenal and responds to fluid administration. The severity of renal abnormality correlates well with degree of hypoxia. The overall mortality in AKI was 12% and the pre-renal non-oliguric type had better prognosis in contrast to intrinsic renal AKI. Intrinsic AKI, oliguria, hyponatremia, reduced creatinine clearance, and abnormal sonographic scan suggest bad prognosis in neonatal AKI secondary to perinatal asphyxia. Newborns having AKI are predisposed to the development of chronic renal failure in the future. Hence, long term follow up of renal function status has to be monitored in these babies. Further studies are required in this including a large sample and broad base to come to an inference.

CONCLUSIONS

Early recognition of AKI is important in babies with HIE to facilitate appropriate fluid and electrolyte management as a stable biochemical milieu is vital.

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