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Original Article

Acute Kidney Injury in Neonates with Perinatal Asphyxia: A Descriptive Analysis

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Abstract

Introduction: Although acute kidney injury (AKI) is one of the complications of perinatal asphyxia, it is not well recognized morbidity in neonates. AKI based on serum creatinine and urine output assessments vary widely. We aimed to study the prevalence and characteristics of AKI among perinatally asphyxiated near term and term neonates. We also evaluated oliguric and non-oliguric AKI on day three of life and relationship of AKI to hypoxic-ischemic encephalopathy (HIE) stages. Further we compared mortality among asphyxiated neonates with and without AKI as well as mortality among oliguric AKI and non-oliguric AKI neonates.

Methods: Neonates with gestation ≥ 35 weeks fulfilling the criteria of perinatal asphyxia were included in the study. The serum creatinine, electrolytes, urine output, presence of HIE and duration of hospital stay were studied.

Results: A total of 67 perinatally asphyxiated neonates were studied. Oliguria was found in nine (13.4%) neonates on day two. Among them, six (66.6%) neonates had normal urine output and three (33.4%) continued to have oliguria by day three. On day three, AKI was found in 32 (47.8%) neonates which was oliguric in three (9.4%) and non-oliguric in 29 (90.6%). AKI was observed in 23 (44.2%) of 52 neonates with HIE, 60% of HIE stage I, 41% of HIE stage II and 33.3% of HIE stage III. Mortality among neonates with AKI was 6.3 (95% CI - 0.7 to 57.1) times greater compared to neonates without AKI. A higher percentage of oliguric AKI neonates expired (2 / 3; 66.6%) compared to non-oliguric AKI neonates (3 / 29; 13.8%).

Conclusions: Among asphyxiated neonates, AKI was observed in 48% on day three. AKI was mostly non-oliguric. AKI especially the oliguric type in asphyxiated neonates contributes to higher mortality.

Introduction

Perinatal asphyxia in near-term and term neonates causes significant morbidity and mortality. The reported incidence varies from 1% to 1.5% at various centers in developed countries.[1] The incidence in developing countries is much higher and deaths up to 28.8% attributable to perinatal asphyxia have been reported.[2]

Asphyxia can lead to multiorgan dysfunction and the kidney is one of the major target organs. Acute kidney injury (AKI) is known to occur in 20% to 70% of these neonates.[2-5] Renal parenchymal injury may occur within a day of a hypoxic-ischemic insult. Prolonged insult may even lead to irreversible cortical necrosis. Heterogeneous response of individual nephrons and variable damage to tubular epithelium results in

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a reduction in glomerular filtration rate (GFR) and decreased tubular fluid flow. When the tubular function is preserved with less reduction of GFR, non-oliguric kidney injury occurs. Abnormal weight gain and electrolyte disturbances associated with AKI may complicate the treatment of asphyxiated neonates. Severe asphyxia and hypoxic-ischemic encephalopathy (HIE) may be associated with higher incidences of AKI. In addition, post-asphyxial AKI especially those associated with oliguria may lead to higher mortality.

Early recognition of kidney injury is likely to facilitate appropriate fluid and electrolyte management and decrease mortality.[5-10] In this context, the present study was conducted to determine the prevalence and characteristics of AKI among perinatally asphyxiated neonates.

Methods

Neonates with ≥ 35 weeks gestation admitted in the neonatal intensive care unit of a tertiary care teaching hospital satisfying the criteria of perinatal asphyxia were included in the study between October 2014 and June 2016. Approval was obtained from the Ethics Committee of the Institution. Informed written consent from the parents was taken. Perinatal asphyxia was considered in a neonate with any one of the following criteria - Apgar score of ≤ 6 at 5 minutes, umbilical cord blood pH ≤ 7.0, features suggestive of hypoxic encephalopathy (Seizures / hypotonia / coma / irritability). Abnormal neurological status was ascertained as per Sarnat stage. Neonates < 35 weeks of gestation, those with renal anomalies or other major congenital malformations, known syndromes, with early onset sepsis, taking aminoglycosides and with respiratory distress syndrome were excluded. AKI was considered if the neonate had serum creatinine ≥ 0.8 mg / dL on day one of life or ≥ 0.6 mg / dL on day three of life.[11] AKI was considered oliguric, if urine output was < 1 ml / kg / hour in a day after 24 hrs of life. HIE was considered in the presence of the following features - hyperalertness, seizures, coma, or tone abnormality. Sarnat's stages were assigned based on standard criteria for HIE as stage I, II and III. Gestational age was classified as preterm: < 37 weeks and term 37 to less than 42 weeks. Potassium levels were considered normal - 3.5 - 5.5 mmol / L, hyperkalemia > 5.5 mmol / L and hypokalemia < 3.5 mmol/L.[1] Sodium levels were considered as normal – 130 - 145 mmol / L, hypernatremia > 145 mmol / L and hyponatremia < 130 mmol / L. Urea level greater than 40 mg / dL was considered elevated. The demographic data and physical examination findings, evidence of other system involvement, and treatment details were recorded. The blood sample at admission and on day three were obtained for estimation of blood urea, serum creatinine, and electrolytes. Biochemical parameters were analysed using Roche / Hitachi Cobas c 501 system. Renal ultrasonography was obtained in these neonates. Urine output was calculated at six hours intervals for the initial 72 hours and if clinically indicated for a longer time. The data were analyzed by software SPSS V20 and P value of < 0.05 was considered statistically significant.

Results

The incidence of perinatal asphyxia during the study period was 7.6 / 1000 live births. Of 108 asphyxiated neonates, 41 were excluded and 67 neonates were further analyzed (Figure 1).

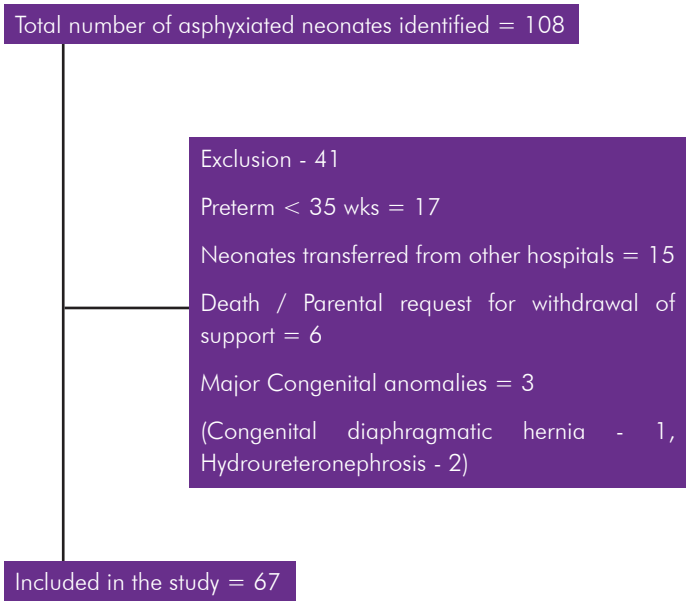

Figure 1: Study flow chart

The demographic details of the study population has been depicted in Table 1.

Table 1: Demographic data (N = 67)

Variable		N (%)
Gender	Male	39 (58.2)
	Female	28 (41.8)
Gestational age	35 – 36 weeks	10 (14.9)
	≥ 37 weeks	57 (85.1)
Birth weight	NBW (≥ 2.5kg)	48 (71.6)
	LBW (< 2.5kg)	19 (28.4)
GA to birth weight	AGA	59 (88.1)
	SGA	8 (11.9)
Mode of delivery	NVD	38 (56.7)
	AVD	3 (4.5)
	ECS	26 (38.8)
Mode of resuscitation	Oxygen	31 (46.3)
	Bag & mask	25 (37.3)
	Bag & tube	11(16.4)

MSAF was noted to be the important risk factor of perinatal asphyxia (26.8%) followed by fetal distress (10.4%) and pre-eclampsia (5.9%). Cord prolapse contributed 3%, and abnormal presentation contributed 2.9% of birth asphyxia. The prolonged second stage of labor, oligohydramnios, antepartum hemorrhage, and gestational diabetes were identified in one case each. Two neonates had two or more risk factors. The biochemical parameters in asphyxiated neonates are represented in Table 2.

Table 2: Distribution of biochemical parameters in asphyxiated neonates (N = 67)

Variable	Day 1	Day 3
Creatinine (mg / dl)		
Mean ± SD	0.9 ± 0.3	0.6 ± 0.4
Range	0.5 - 2.5	0.2 - 2.9
Median (75^{th}, 25^{th} IQR)	0.9 (1.1, 0.8)	0.5 (0.8, 0.5)
Urea (mg / dl)		
Mean ± SD	18.9 ± 9.1	24.1 ± 14.1
Range	8 - 59	5 - 61
Median (75^{th}, 25^{th} IQR)	16.0 (21, 14)	23 (33, 12)
Sodium (mEq / L)		
Mean ± SD	134.7 ± 5.8	135.6±6.8
Range	119 - 152	115 - 146
Median (75^{th}, 25^{th} IQR)	135 (138 , 131)	137 (141, 132)
Potassium (mEq / l)		
Mean ± SD	4.7 ± 0.9	4.6 ± 0.8
Range	3.3 - 7	2.9 - 7.1
Median (75^{th}, 25^{th} IQR)	4.8 (5.4, 4.3)	4.7 (5.3, 4.0)

Among 67 neonates, 52 (77.6%) had AKI on day one with a mean creatinine value of 1.05 ± 0.3 mg / dl (Table 3). Among 52 neonates with AKI on day one, creatinine normalized on day three in 24 neonates and creatinine remained elevated in 28 neonates. Four neonates having normal creatinine on day 1 were found to have elevated creatinine on day three.

The mean urine output was 1.8 ± 0.8 ml / kg / hour on day two and 2.5 ± 1.9 ml / kg / hour on day three. Among 67 asphyxiated neonates, nine (13.4%) had oliguria on day two and four (5.9%) had oliguria on day three. Among nine oliguric neonates on day two, six (66.6%) had normal urine output on day three, and three (33.3%) continued to have oliguria. One neonate developed oliguria on day three. Two neonates persisted to be oliguric beyond 72 hrs even after supportive therapy. A comparison of the mean serum urea, sodium, and potassium levels of day one among neonates with AKI and without AKI was statistically not significant. Among 52 neonates with AKI, three had elevated urea and 11 had elevated potassium.

Table 3: Comparison of biochemical parameters with and without AKI on day one.

Parameter	AKI (52)	No AKI (15)	P - value
Urea (mg / dL):			
Mean ± SD	19.3 ± 10.2	17.5 ± 3.4	
Range	8, 59	11, 23	
Median (75^{th}, 25th IQR)	16 (22.7, 13)	17 (20, 15)	0.55 (NS) $
Sodium (mmol / L)			
Mean	134.4 ± 5.6	135.8 ± 6.7	
Range	119, 145	125, 152	0.67 (NS) $
Median (75^{th}, 25^{th} IQR)	135 (138,131)	13 (139,132)	
Potassium (mmol / L)			
Mean	4.7 ± 1.0	4.9 ± 0.7	
Range	3.3, 7.0	4.0, 7.0	0.61 (NS) $
Median ($75^{th,}$ 25^{th} IQR)	4.8 (5.2, 4.2)	5.0 (5.4, 4.4)	

$ By Mann-Whitney test

Table 4: Creatinine-based AKI among different stages of HIE

HIE stages	Day 1		Day 3	
	AKI (52)	No AKI (15)	AKI (32)	No AKI (35)
No HIE (N =15)	10	5	9	6
HIE stage I (N = 10)	7	3	6	4
HIE stage II (N = 39)	33	6	16	23
HIE stage III (N = 3)	2	1	1	2

Among 67 asphyxiated neonates, the HIE stages are shown in Table 4. AKI did not correlate with the severity of HIE stages (P = > 0.05). Among 67 asphyxiated neonates, 32 (47.8%) had AKI on day three based on serum creatinine and their mean creatinine value was 0.98 ± 0.53 mg / dL. Among 32, three (9.4%) had oliguric AKI and 29 (90.6%) had non-oliguric AKI. Among three oliguric AKI neonates, two neonates had oliguria from day two and one neonate developed oliguria on day three.

Among the 32 perinatally asphyxiated neonates with AKI, five neonates expired and among 35 neonates without AKI, one neonate expired (Table 5). Mortality among neonates with AKI

was 6.29 (95% CI - 0.69 to 57.14) times more compared to neonates without AKI. Neonates who died had HIE stage 2. The other significant comorbidities in neonates who died included, severe MAS with severe PAH in four and multiorgan dysfunction in two. Among 32 AKI neonates, five expired with a mortality rate of 15.6%. Two out of three oliguric AKI (66.6%) died compared to three out of 29 (13.8%) non oliguric neonates who died. Overall, oliguric AKI neonatal deaths constituted 6.2% and non-oliguric AKI neonatal death constituted 9.4%. The pre-discharge serum creatinine was elevated (> 0.6 mg / dL) in only three neonates.

Table 5: The outcome of neonates with and without day three creatinine-based AKI

	With AKI (N = 32)	Without AKI (N = 35)
Duration of NICU stay (days)*		
Mean ± SD	10.7 ± 6.7	11.09 ± 5.9
Range	3- 33	3-30
Median (IQR 75th, 25th)	10 (14,6)	10 (14, 6)
Duration of hospital stay (days)*		
Mean ± SD	12.9 ± 7.2	14.38± 8.7
Range	4-37	7-51
Median (IQR 75th, 25th)	10 (17,9)	12.5 (15.2, 9)
Deaths	5	1

*Six deaths and two discharged at parental request after day 3 of life were excluded

Discussion

Perinatal asphyxia is one of the important causes of AKI in neonates.[1,12] The incidence of AKI varies from 9% to 61% in asphyxiated full-term infants.[12,13] AKI in severely asphyxiated neonates was non oliguric in 60%, oliguric in 25% and anuric in 15%.[12] Hyperuricaemia, hyperuricosuria, and higher urinary protein concentrations were also observed in asphyxiated neonates. These markers demonstrated renal tubular damage and such neonates exhibited an increased renal cortical echogenicity in ultrasonography.[14] Perinatal hypoxia causes damage to nephrons, acute tubular necrosis and sometimes may lead to renal vein thrombosis.[15] The compromised sodium reabsorption capacity of the distal convoluted tubule and higher urinary sodium loss causes hyponatremia. Syndrome of inappropriate antidiuretic hormone secretion and partial aldosterone resistance may also contribute to hyponatremia. Hyponatremia leads to hypovolemia and compromise renal functions further. In neonates, the compromised GFR is sufficient to permit growth and the clearance of toxic metabolites under normal conditions, but during challenging conditions like perinatal asphyxia, the reduced GFR limits the compensatory ability of the neonate.[16] The determination of renal impairment by measuring urea and creatinine was also suggested as a criterion for the neurological prognosis.[17] Serum creatinine level is still the most widely used marker to define AKI in the neonate despite its limitations.[18]

The present study has found important characteristics of AKI in perinatal asphyxia. The day three creatinine and urine output are likely to give more useful information regarding AKI. The mortality was more common in asphyxiated neonates with AKI especially those with oliguric type. Identifying AKI in asphyxiated neonates would help in better management especially the daily fluid therapy.

The mean serum creatinine level on the day on day one and day three were 0.9 ± 0.3 mg / dL and 0.6 ± 0.4 respectively. Mean serum sodium and potassium levels on day one and day three were mostly the same. In contrast, Roy et al in their study observed that mean urea and creatinine levels were higher on day three when compared to day one with no significant difference in levels of sodium and potassium on day one and day three.[19]

In the present study, 32 of 67 neonates had AKI on day three based upon serum creatinine with a mean creatinine of 0.98 ± 0.53 mg / dL. Among 32, three (9.4%) had oliguric AKI and 29 (90.6%) had non-oliguric AKI. In a study by Roy et al, 56% of asphyxiated neonates had AKI on day three with a mean creatinine of 1.62 ± 0.3 mg / dL.[19] In another study, 61% of asphyxiated neonates had AKI on day three with a mean creatinine of 1.4 ± 0.6 mg / dL.[20] Kaur et al reported AKI incidence of 41.7% in asphyxiated neonates, with an incidence of 9.1% in infants with moderate asphyxia and 56% among infants with severe asphyxia.[21] Among 67 asphyxiated neonates, four (5.9%) had oliguria on day three. In a study by Karlowicz et al, 25% of asphyxiated neonates had oliguria after 24 hours of life.[9]

Few researchers attempted to find the relationship between AKI and HIE stages. AKI did not correlate with the severity of HIE stages (P = > 0.05) in the present study. This could be because of the small number of neonates in the HIE stage 3 group. Nouri et al studied AKI in 87 neonates with HIE.[17] Stage I was found in nine neonates (10.3%), stage II in 67 (77%), and stage III in 11 (12.6%). AKI was found in 15 neonates (17.2%) of whom 10 belonged to HIE stage 2. Authors reported eight deaths of whom three had AKI. A study by Alaro et al reported that among 60 neonates with HIE on day three, 42.9% had

AKI in HIE stage III and 9.7% had AKI in HIE stage II.[22]

Among 32 AKI neonates, five expired with a mortality rate of 15.6%. Oliguric AKI neonatal deaths constituted 6.2%. A previous study reported 61.5% mortality in asphyxiated neonates with AKI.[23] Mortality rate in perinatal asphyxia associated AKI was 71.4 % in another study.[22] AKI is likely to influence mortality in critically ill neonates including asphyxia.[24] Among the survivors, the pre-discharge serum creatinine was elevated in only three neonates. A good renal outcome among the survivors of asphyxia-related AKI was earlier reported by Nouri et al.[17]

This study had few limitations. This was a single centre study. Though the mortality was found to be higher in oliguric AKI, we could not assess whether this parameter can independently predict mortality. Multiple logistic regression model may be helpful in assessing such predictive characteristic.

Conclusions

AKI was observed in 48% of asphyxiated neonates. AKI was mostly non-oliguric. AKI especially the oliguric type in asphyxiated neonates contributed to higher mortality. Continuous monitoring of the asphyxiated neonates regarding creatinine, electrolytes, and urine output from day one onwards helps in identifying the AKI and choice of appropriate fluid regimen.

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