

Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia

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Abstract

Background: The kidney is the most damaged organ in asphyxiated full-term infants. The severity of its damage is correlated with the severity of neurological damage. We determined the prevalence of perinatal asphyxia-associated acute kidney injury (AKI).

Methods: We conducted a prospective cohort study including 60 full-term neonates admitted at the Kenyatta National Hospital newborn unit (NBU) in Nairobi with hypoxic ischaemic encephalopathy (HIE) from June 2012 to November 2012. Renal function was assessed by measuring serum creatinine on day 3 of life. AKI was defined by a level of creatinine above 133 $\mu\text{mol/l}$. The degree of neurological impairment was determined daily until patient discharge, death or day 7 of life.

Results: Of the 60 infants 36.6% had HIE I, 51.6% HIE II and 11.8% HIE III. The prevalence of AKI was 11.7%. There was a 15 fold increase risk of developing AKI in HIE III versus HIE I, $p=0.034$. Mortality rate in perinatal asphyxia associated AKI was 71.4% with a 24 fold increase risk of death in neonates with AKI, $p=0.001$.

Conclusions: AKI is common and associated with poorer outcomes in perinatal asphyxia. Larger studies need to be done to correlate maternal factors and perinatal asphyxia-associated AKI.

Key words: moderate perinatal asphyxia, severe perinatal asphyxia, hypoxic ischaemic encephalopathy, neonatal kidney dysfunction, neonatal neurological dysfunction.

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Introduction

Perinatal asphyxia is defined by the World Health Organisation (WHO) as "Failure to initiate and sustain breathing at birth." (1) There is a high incidence of AKI among the asphyxiated term infants, (50 – 72%). (2,3). The presence of perinatal asphyxia and its severity appear to correlate with increasing incidence of AKI. (2,4) Asphyxia is an important cause of AKI and transient kidney impairment with adverse effects, especially in the five days of birth. (5,6) The kidney is the most damaged organ in asphyxiated full-term infants. (6) There lacks an internationally acceptable definition of AKI in neonates. Most of the previous investigators have defined AKI in neonates as serum creatinine above 133 $\mu\text{mol/l}$. (7,8)

The objective of this study was to determine the prevalence of acute kidney injury using serum creatinine above 133 $\mu\text{mol/l}$ and short term outcomes of moderate to severe perinatal asphyxia-associated acute kidney injury.

Methods

This was a prospective cohort conducted at the KNH NBU over a 6 month period (June 2012 to November 2012). All term neonates with moderate to severe perinatal asphyxia admitted within 24hrs of delivery into the NBU. The 56 consecutive term newborns that satisfied the inclusion criteria were enrolled after written informed consent was obtained from either of the parents having given them clear explanation of the purpose of the study, expected benefits and potential harms. Ethical approval was obtained from the Ethical Review Committee, KNH. Newborns with malformation syndromes and those who died within 3 days of admission were excluded from the study.

Maternal and neonatal data was captured using pre-tested questionnaires and forms. Perinatal asphyxia was defined as failure to initiate and sustain breathing at birth (1), clinical evidence of HIE (9) and Apgar score less than 7 at 5 minutes. Gestational age was determined us-

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ing the Finnström score.(10)

Emergency care and resuscitation was a priority to any other procedures. Study details were given to the immediate caregivers. No beneficial treatment was withheld from the study subjects. All information about the patient was treated with the strictest confidence.

The neonate's length, body weight and head circumference were measured on admission. Neonatal body weight and the degree of neurological impairment were determined according to Sarnat classification daily until patient discharge, death or day

7 of life. Serum creatinine values were determined on day 2 and 3 of life by heel sampling of 0.5ml to 1ml into a microtainer. The sample was then centrifuged within 2 hours and analysed using Cobas Integra machine using the compensated Jaffé method.

Statistical analysis

Statistical analysis was conducted using statistical products and services solutions (SPSS) software version

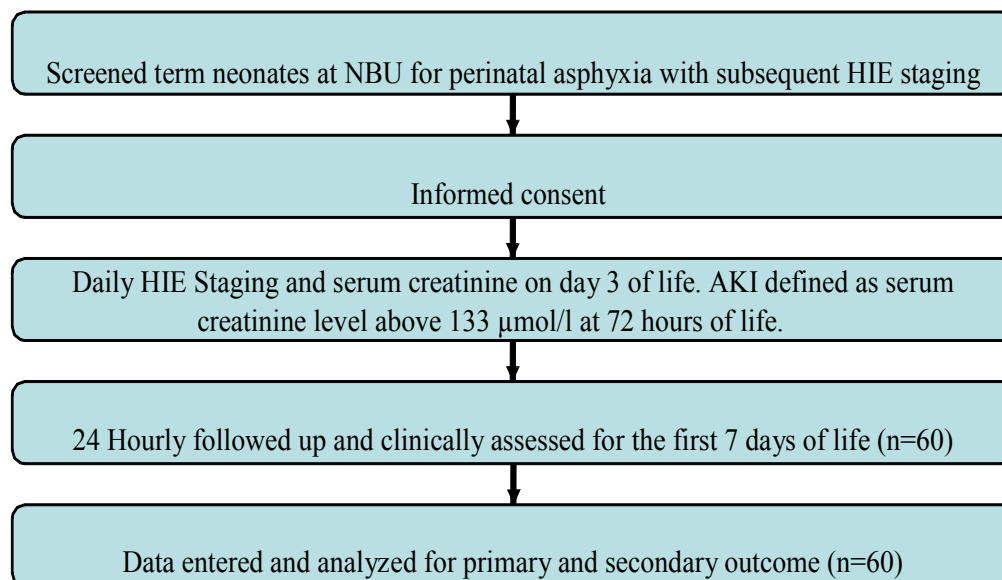
17.0. Descriptive data were presented as numbers (percentages) or mean (standard deviation), as appropriate. Characteristics were compared using Fischer's exact test for dichotomous variables and Wilcoxon rank-sum test for continuous variables. Test of associations between the neonatal/ maternal factors and the study outcomes were performed using Chi-square test for categorical variables and comparisons of means and medians was done using student's test and Mann Whitney U test respectively. A p-value of 0.05 was considered statistically significant.

Results

Of the 968 newborns admitted into the KNH NBU during the study period, 60 infants met the inclusion criteria and were analysed as shown in figure 1.

The mean weight was 3373 g (SD=427.3), length 52.3 cm (SD=2.1), clinical gestation 39.4 weeks (SD=0.87) and head circumference 34.8 cm (SD=1.6). The neonates weight ranged from 2620 to 4600 g. Only 9% of the neonates admitted had a severe Apgar score (0-3), while 91% had a moderate Apgar score (4-6). Most of

Figure 1: Flow chart showing the patient recruitment process



the neonates were delivered in KNH (76%), 24% from other facility but none was delivered at home. Most of the neonates were delivered by the vaginal route (63%), 33% via caesarian section and 4% via vacuum extraction. Only 40% of the neonates were resuscitated at birth and 18% intubated and mechanically ventilated.

Majority of the mothers (86%) were married and 53% were primigravidae. Majority of the mothers were employed (77%) versus 23% unemployed. Only 15% of the mothers had a level of education of primary school and below versus 75% who had attained secondary level of education and above. Almost all the mothers (90%) reported having attended antenatal clinic (ANC) visit with 75% having attended ANC more than twice and 15% attending only once.

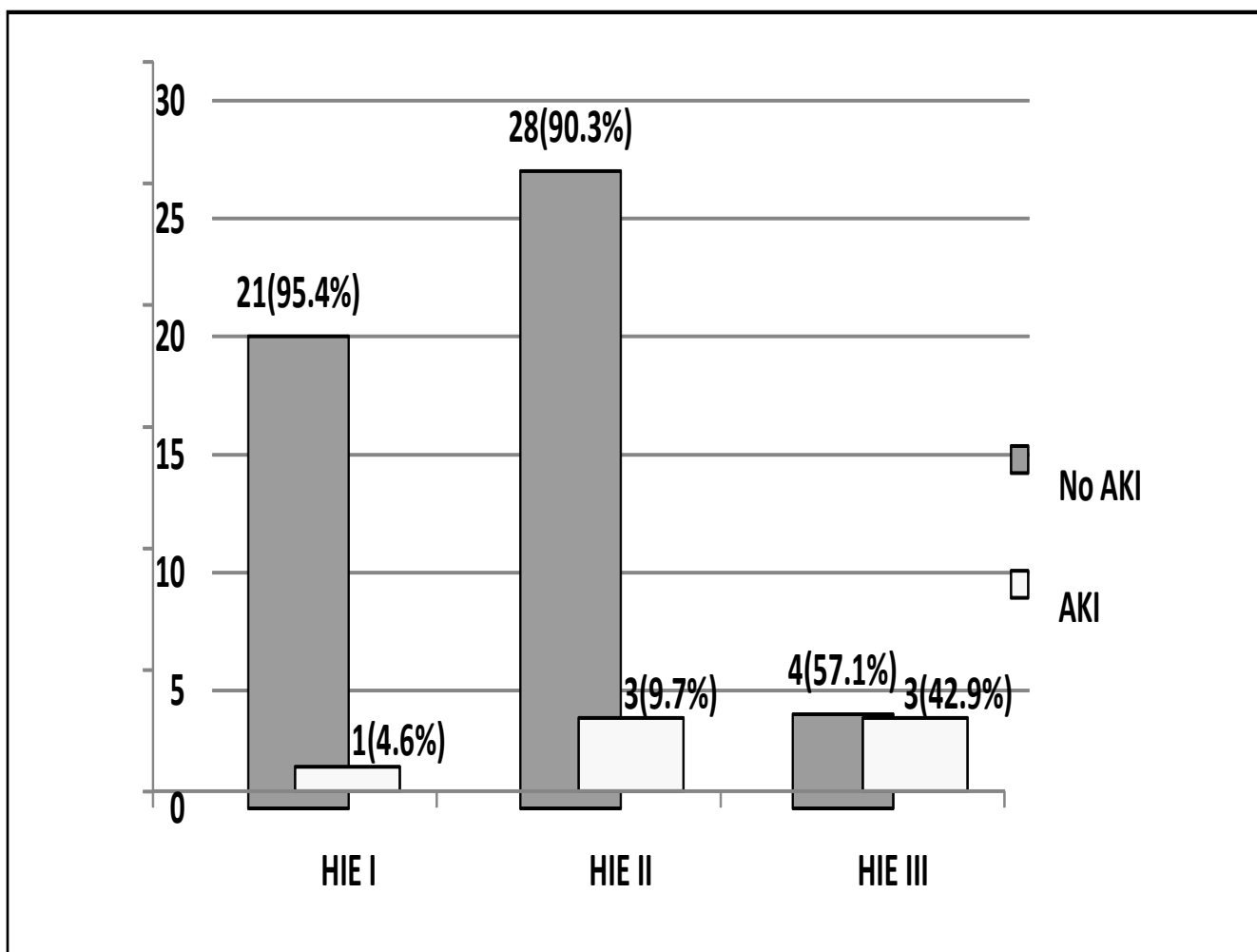
The degree of perinatal asphyxia was staged using Sarnat and Sarnat staging of Hypoxic Ischaemic Encephalopathy (HIE) on admission. Majority 31(52%) had HIE II, 22 (36%) HIE I and 7 (12%) HIE III. Out of the neonates with AKI, 11.1 % (4/36) of the males were affected versus 12.5 % (3/24) of the females. 7 out of 60 neonates met criteria for AKI on day 3. Translates to a prevalence of 11.7%

AKI was highest in the neonates with HIE 3 (42.9%) on day 3 of life and lowest in the neonates with HIE 1 (4.6%) as per figure 2.

There was no statistically significant association between newborn, maternal characteristics and AKI (table 1 and 2).

Table 1: Tests of Association between Neonatal characteristics and AKI

Figure 2: Correlation between HIE and AKI



According to table 3, the mortality rate in perinatal asphyxia associated AKI was 71.4 %. There was a 15 fold increase risk of developing AKI in HIE III compared

to HIE I, $p=0.034$ with 95% CI (1.2-183.6). There was 24 fold increase risk of death in AKI, $p=0.001$ with 95% CI (3.7-157). Median day of death in neonates with AKI was 4.5 days

		AKI (n= 7)	No AKI (n= 53)	P value
Sex	Male	4 (57%)	32 (60%)	1.000
	Female	3 (43%)	21 (40%)	
Apgar	Moderate	6 (86%)	46 (87%)	1.000
	Severe	1 (14%)	7 (13%)	
Resuscitation		5 (83%)	19 (45%)	0.188
Place of delivery	KNH	5 (71%)	40 (75%)	1.000
	Other health facilities	2 (29%)	13 (25%)	
Intubation		1 (14%)	6 (12%)	1.000

*Significant difference ($p < 0.05$)

The outcome of the neonates with AKI versus no AKI by day 7 of life was: discharged 14% versus 46 %, died 71% versus 9% and still admitted in NBU 14% ver-

sus 30%. The greater mortality rate (71.4 %) in the neonates with AKI may be high due to the small sample size number.

Discussion

Table 2: Tests of Association between Maternal characteristics and AKI

		AKI (n=7)	NoAKI (n= 53)	P value
Maternal Age {Median (IQR)}		29 (19-33)	27 (24-29)	0.630
Marital status	Single	1 (14%)	7 (13%)	0.522
	Married	6 (86%)	46 (87%)	
Occupation	Employed	4 (57%)	42 (79%)	0.075
	Unemployment	3 (43%)	11 (21%)	
Maternal Fever		1 (14%)	3 (6%)	0.220
APH		1 (14%)	5 (11%)	1.000
Level of education	Primary and below	2 (29%)	10 (19%)	0.330
	Secondary and above	5 (71%)	43 (81%)	
Mode of delivery	Vertex Vaginal	3 (43%)	34 (64%)	0.494
	Breech V aginal	0 (0%)	1 (2%)	
	Caesarean	4 (57%)	16 (30%)	
	Vacuum extraction	0 (0%)	2 (4%)	

According to the Acute Kidney Injury Network (AKIN), AKI is an absolute increase in serum creatinine of $\geq 26.4\mu\text{mol/l}$ (or a percentage increase in serum creati-

nine of at least 50%) over two consecutive days.⁷ Creatinine in the normal newborn at term by Schwartz is $79\mu\text{mol/l}$ at day 1 and drops to $44\mu\text{mol/l}$ at day

Table 3: Short-term outcomes of perinatal asphyxia associated AKI

	AKI (N=7)	No AKI (n=53)	OD (95% CI)	P Value
HIE I	1 (14%)	21 (39%)	1.00	
II	3 (43%)	28 (53%)	2.22 (0.2-23.0)	0.5
III	3 (43%)	4 (8%)	15 (1.2-183.6)	0.034*
Discharge in days {Median (IQR)}	5 (4-7)	5 (4-7)		0.56
Mortality	5 (71%)	5 (9%)	24 (3.7- 157)	0.001*
Time of death { Median (IQR)}	4.5 (3.5 -5)	4 (2-4)		0.45

*** significant difference (P < 0.05)**

HIE – Hypoxic Ischaemic Encephalopathy

5.11 Before 48h of life, the serum creatinine reflects that of the mother. 8

Studies by Jayshree 12, Nouri 14 and Gupta 2 chose the threshold of $90\mu\text{mol/l}$ for serum creatinine at 48 hours of life. Studies by Karlowicz 3 Kaur 13 chose the serum creatinine threshold of $133\mu\text{mol/l}$ at 48 hours to make a diagnosis of AKI. In our study, the threshold of $133\mu\text{mol/l}$ for creatinine at 72 hours of life was chosen in order to increase our possibility of diagnosis as there would be a marked reduction in the maternal creatinine level by then.

There is a high incidence of AKI among the asphyxiated term infants (7 – 72%). 2,3 AKI after perinatal asphyxia was noted in 42% of cases for Martin-Ancel 4, 47% to Gupta 2, 68% for Aggrawal 8, 70% to Gluckman¹⁵, 17.2 % Nouri¹⁴ and 33% in our study. Our study noted 11.7% prevalence rate hence lying within the range of most of the studies done. The prevalence rate may have been much higher than the Tunisia study

if serum creatinine was sampled at 48 hours and threshold of $90\mu\text{mol/l}$ used. The available studies show that the prevalence rates were similar in both resource poor and resource rich areas proving that AKI in perinatal asphyxia is a global problem.

The presence of perinatal asphyxia and its severity appears to correlate with increasing incidence of AKI.^{2,4} Nouri¹⁴ who had two thirds of newborns with AKI had grade II and 1/3 with AKI had grade III. However in his study no renal impairment was observed in newborns with grade I. The difference was not statistically significant ($p = 0.13$). Gupta 2 however showed that blood urea and serum creatinine were significantly higher in asphyxiated and HIE babies compared to the control group ($P < 0.001$) and ($P < 0.05$) respectively hence showing the correlation between AKI and HIE. Kaur¹³ showed that AKI developed in 1 out of 11 infants (9.1%) with moderate asphyxia and in 12 of 25 (56%) with severe asphyxia. Our study noted a 15 fold

increase risk of developing AKI in HIE III compared to HIE I, $p=0.034$ with 95% CI (1.2-183.6). However there was no correlation between HIE II and I ($p=0.50$), and this could be explained by the small sample size. AKI was highest in the neonates with HIE 3 (42.9%) on day 3 of life and lowest in the neonates with HIE 1 (4.8%).

The small sample sizes in most studies have been a major hindrance in realizing associations between neonatal or maternal characteristics and AKI. Some authors have shown a significant association between low Apgar score at the 5th min and AKI, with a level of significance as low as $p = 0.0013$ by Nouri. 4,14 In our study 14% of the patients with severe Apgar score had AKI while majority (86%) of the patients with moderate asphyxia had AKI. This could be explained by the fact that many of the patients who have severe asphyxia die before day 3 of life and hence are not included in the study. However, we found no significant correlation between Apgar and AKI ($p=0.473$).

The mortality rates of perinatal asphyxia-associated AKI ranges between 2% and 20 % ($p=0.11$) 2, 14,13 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 death¹⁶

The cause of death for patients diagnosed with AKI may not be the same as the cause of AKI. The mortality rate depends on other associated conditions, e.g. other organ failure, particularly cardiac failure, HIE and serious infection hence the difficulty in quoting the exact mortality rate secondary to AKI in our study and the previous ones.

1 out of every 8 neonates with moderate and severe perinatal asphyxia is likely to develop AKI with 5 out of 7 of these neonates likely to die by day 4 of life. AKI correlates with HIE, and the risk of developing AKI is higher with a more severe form of HIE. The neonates who have HIE III have a 15 times increased risk of developing AKI. The neonates who develop AKI have a 24 times increased risk of death. 1 out of 7 of the neonates who develop AKI will be discharged by day 7 of life. Clinicians should therefore endeavor to diagnose AKI and institute relevant measures from day 3 of life. Larger studies need to be done to correlate maternal factors and perinatal asphyxia-associated AKI.

Acknowledgements

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