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Acute Kidney Injury Among Asphyxiated Neonates In Sokoto, North West Nigeria.

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Abstract
Background:
Birth asphyxia and its attendant complications remain a common problem in our neonatal intensive care units. Compelling evidence from various epidemiologic studies shows that Acute Kidney Injury (AKI) is indeed one of the commonest complications of birth asphyxia. The kidneys are sensitive to oxygen deprivation, renal insult may occur within few hours of hypoxic-ischemic episode, which if prolonged could lead to irreversible cortical and or tubular necrosis.
Aim*: To determine the prevalence and factors associated with AKI among asphyxiated term neonates in Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto, Nigeria*
Materials and methods: *One hundred and nineteen asphyxiated term neonates admitted into the special care baby unit of UDUTH Sokoto participated in the study. Birth asphyxia was defined as failure to initiate and sustain breathing at birth with Apgar scores ≤ 5 at 5 minutes in the presence of arterial cord blood pH < 7 and base deficit >12mmol. Blood samples were taken for arterial blood gas analysis within one hour of life. Moderately and severely asphyxiated neonates who satisfied the inclusion criteria were consecutively recruited into the study and serum creatinine assay was done on day 3 and day 5 of life. AKI was defined as a rise in serum creatinine ≥ 0.3mg/dl over 48 hours. Quantitative variables such as birth weight, length, occipitofrontal circumference (OFC) were expressed using mean, standard deviation and range, while qualitative variables like gender, mode of delivery and grade of asphyxia were summarised using frequency and percentages. Chi-square and fisher's exact tests were applied to determine if any relationship exists between sociodemographic/clinical factors and AKI. A p-value of < 0.05 was considered statistically significant.*

Results: *Of the 119 asphyxiated term neonates 74 (62.2%) were males while 45 (37.8%) were females giving a M:F ratio of 1.6:1. Majority 96 (80.7%) of the subjects had normal birth weight with a mean birth weight of 3.1 ± 0.6kg. The mean gestational age recorded was 38.2 ± 1.1 months The prevalence of AKI in the study subjects was 42.9%. The grade of birth asphyxia was significantly associated with AKI with a prevalence odds ratio of 7.2 (95CI 2.8-18).*
Conclusion: *The prevalence of AKI in asphyxiated term neonates in UDUTH Sokoto was high and the grade of birth asphyxia was found to be significantly associated with AKI.*
Keywords =*acute kidney injury, neonates, birth asphyxia, AKI, Sokoto, Nigeria*

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I. Introduction

Birth asphyxia is defined as the marked impairment of gas exchange leading, if prolonged to progressive hypoxemia, hypercapnia and significant metabolic acidosis.[1] It is a failure to initiate and sustain breathing at birth.[2] It remains a common neonatal problem and a significant cause of morbidity and mortality.[3] It ranks as the second most important cause of neonatal deaths.[4]. Its diagnosis is made based on Apgar score and umbilical blood sampling; an Apgar score of ≤ 7 at 5 minutes in the presence of metabolic acidosis which is defined by an arterial cord blood pH < 7.0 and a base deficit of >12mmol/L.[5, 6 7]

Birth asphyxia and its attendant complications remain a common problem in our neonatal intensive care units. There is compelling evidence from various epidemiologic studies that shows that acute kidney injury is indeed one of the commonest complications of birth asphyxia.[8-11]

Acute Kidney Injury (AKI) is defined as an abrupt decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function).[12] It is a potentially reversible deterioration in kidney function resulting in accumulation of nitrogenous waste and derangements in fluid and electrolyte homeostasis.[13] Its diagnosis is traditionally based on a rise in serum creatinine and/or a fall in urine output.[14]

Asphyxia can lead to multi-organ dysfunction by causing a 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 is common in asphyxiated neonates.[15] New-borns with AKI following neonatal asphyxia have an ominous prognosis particularly those with oliguric AKI.[16]

The kidneys are sensitive to oxygen deprivation and renal insult may occur within few hours of hypoxic-ischemic episode, which if prolonged could lead to irreversible cortical and or tubular necrosis.[17] Additionally, new-born babies are more susceptible to AKI compared to older children because they have low glomerular filtration rate, high renal vascular resistance, high plasma renin activity and decreased reabsorption of sodium in the proximal tubules.[18] AKI in the neonatal period has been reported as one of the risk factors for developing Chronic Kidney Disease (CKD) and hypertension in later years, a long term outcome that will place an enormous economic burden on the family and the society as a whole and poor quality of life for the patient.[19]

The current definitions of AKI are based on the Risk, Injury, Failure, Loss and End-stage renal disease (RIFLE), Acute kidney injury network (AKIN) and Kidney-Disease; Improving Global Outcome (KDIGO) criteria.[20, 21] The use of standardized definitions of AKI has allowed comparison between studies and was a fundamental first step that has been integral to the study of AKI in medicine.[22] One of such standardised definition of AKI described in details by Jetton, and Askenazi,[23] is based on a modification of the KDIGO definition termed the Neonatal modified KDIGO criteria.

The Neonatal modified KDIGO criteria defines neonatal AKI:

- Increase in serum creatinine ≥ 0.3mg/dl (≥ 26.5µmol/l) within 48 h or;
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or;
- Urine volume < 0.5ml/kg/h for 6 h.

Definition of terms

1. Neonatal period: defined as the first 28 days of life.
2. Acute kidney injury: defined by a rise in serum creatinine of ≥ 0.3mg/dl over 48 hours, i.e between days 3 and 5.
3. Moderate asphyxia: Apgar score 4 or 5 in the presence of arterial cord blood pH < 7and base deficit > 12mmol.
4. Severe asphyxia: Apgar score ≤ 3 in the presence of arterial cord blood pH < 7and base deficit > 12mmol.

II. Methods

The study is part of a descriptive cross-sectional study carried out in the Special Care Baby Unit (SCBU) of the Department of Paediatrics Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto, Nigeria among 119 term asphyxiated neonates. Moderately and severely asphyxiated babies with Apgar scores ≤ 5 at 5 minutes, arterial cord blood pH of < 7.0, and a base deficit of >12mmol were recruited into the study, in the absence of any exclusion criteria. Neonates with mild birth asphyxia, obvious major congenital malformation(s) and neonates whose mothers had documented abnormal renal function or whose mothers were on nephrotoxic medications were all excluded from the study. Arterial blood gas (ABG) analysis of cord blood was done using a portable point of care ABG machine within one hour of delivery. Blood was collected on the 3rd and 5th day of life for serum creatinine assay in the chemical pathology laboratory of UDUTH Sokoto. AKI was defined as a rise in serum creatinine ≥ 0.3mg/dl over 48 hours. SPSS version 23 and 2016 Microsoft Excel were used for data analysis. Quantitative variables such as birth weight, length, occipitofrontal circumference (OFC) were expressed using mean, standard deviation and range, while qualitative variables like gender, ethnicity, religion, mode of delivery and grade of asphyxia were summarised using frequency and percentages presented in tables. Chi- square and fisher's exact tests were applied to determine if any relationship exists between sociodemographic/clinical factors like birthweight, gender, mode of delivery, socioeconomic status and AKI. A p-value of < 0.05 was considered statistically significant

III. Ethical Considerations

Ethical approval was obtained from the Health Research and Ethics committee of UDUTH Sokoto before embarking on the study. The study was at no cost to the participants. Care of the new born was not compromised in any way if the parents/legal guardian declined participation. Data obtained was treated with utmost confidentiality. All parents/legal guardians were counselled and required to sign the written informed consent form. Neonates with AKI were promptly managed according to standard protocol by the neonatologists and paediatric nephrologists. At discharge, they were referred to the paediatric nephrologists for long term follow up and continuous monitoring of renal function.

IV. Results

Of the 119 moderately and severely asphyxiated term neonates studied, 74 (62.2%) were males and 45 (37.8%) were females with a M:F ratio of 1.6:1. More than half of them 67 (56%) were from a low socio-economic class, 27 (22.7%) of the study subjects were from an upper socioeconomic class, while 25 (21%) were from the middle socioeconomic class. Majority 96 (80.7%) of the subjects had normal birth weight with a mean birth weight of 3.1 ± 0.6kg. The mean length of the study subjects was 50.5 ± 2cm, while the mean OFC was 35.2 ± 2.1cm. The mean gestational age recorded was 38.2 ± 1.1 months.

Table 1 shows the clinical characteristics of the study subjects. There were 18 (15.2%) SGA neonates, as majority 95 (79.8%) were AGA. An almost equal proportion of neonates were delivered via spontaneous vaginal delivery and caesarean section respectively, while only 12 (10.1%) were delivered via assisted vaginal delivery. Majority 86 (72.3%) of the neonates recruited into the study were moderately asphyxiated.

Table 1: Clinical characteristics of the study subjects

Variables	Frequency (n)	Percent (%)
Birth weight (kg)		
<2.5	14	11.8
2.5-4.0	96	80.7
>4	9	7.6
Mean birth weight =3.1 ± 0.6kg		
Weight for gestational age		
SGA	18	15.2
AGA	95	79.8
LGA	6	5.0
Mode of delivery		
Spontaneous vaginal delivery	52	43.7
Caesarean Section	55	46.2
Assisted vaginal delivery	12	10.1
Grade of asphyxia		
Moderate	86	72.3
Severe	33	27.7
GA = Gestational Age, SGA = Small for Gestational Age, **AGA =** Appropriate for Gestational Age, **LGA =** Large for Gestational Age,		

Table 2 shows the serum creatinine levels recorded in the study subjects on day 3 and 5 of life. The mean serum creatinine recorded on days 3 and 5 were 1.1mg/dl and 1.3mg/dl respectively. The change in creatinine levels over 48 hours ranged from 0.1mg/dl to 7.6mg/dl with a mean of 0.4 ± 1.1mg/dl.

Table 2: **Mean Serum Creatinine levels**

Serum creatinine	Mean (mg/dl)	SD	Minimum	Maximum
Day 3 Serum creatinine	1.1	0.7	0.3	3.5
Day 5 Serum creatinine	1.3	1.1	0.2	8.0
Increase in creatinine over 48hrs	0.4	1.1	0.1	7.6
SD = Standard Deviation				

A total number of 51 term asphyxiated neonates had serum creatinine rise of ≥ 0.3mg/dl over 48 hours, i.e between days 3and 5, giving an AKI prevalence of 51/119 (42.9%)-Table 3

Table 3: Prevalence of AKI among asphyxiated neonates

Serum Creatinine change in 48hrs	Frequency (n)	Percentage (%)
Increase of equal or ≥ 0.3mg/dl (≥ 26.5µmol/l)	51	42.9
Increase of < 0.3mg/dl (< 26.5µmol/l)	48	40.3
No change in creatine or decrease in creatinine	20	16.8
Total	119	100

Table 4 shows the association between AKI and some sociodemographic/clinical factors. The degree of asphyxia was found to have a statistically significant association with AKI (p <0.0001) with a prevalence odds ratio of 7.2 (95CI 2.8-18). Severely asphyxiated term neonates are seven times more likely to have AKI than the moderately asphyxiated ones. Factors like gender, social class, birth weight and mode of delivery were not found to be significantly associated with AKI-Table 4

Table 4: Association between AKI and some socio-demographic/clinical factors (n=119)

Variables	Creatinine		Test statistic*	p value	POR (95% CI)
	AKI	No AKI			
	n (%)	n (%)			
Gender					
Male	33 (44.6)	41 (55.4)	0.241	0.623	
Female	18 (40.0)	27 (60.0)			
Social class					
Upper class	10 (37.0)	17 (63.0)	0.775	0.679	
Middle class	10 (40.0)	15 (60.0)			
Lower class	31 (46.3)	36 (53.7)			
Asphyxia					
Severe	25 (75.8)	8 (24.2)	20.183	**< 0.0001**	**7.2 (2.8 -18.0)**
Moderate	26 (30.2)	60 (69.8)			
Birth weight (kg)					
<2.5	4 (28.6)	10(71.4)	Fisher's exact	0.397	
2.5-4.0	44 (45.8)	52 (55.2)			
>4.0	3 (33.3)	6 (66.7)			
Weight for GA					
SGA	8 (44.4)	10 (55.6)	Fisher's exact	1.000	
AGA	41 (43.2)	54 (56.8)			
LGA	2 (33.3)	4 (66.7)			
Mode of delivery					
Vaginal	26 (50.0)	26 (50.0)	2.019	0.365	
Caesarian section	21 (38.2)	34 (61.8)			
Assisted Vaginal	4 (33.3)	8 (66.7)			

* = Pearson's Chi square, **POR** = Prevalence Odds Ratio, **CI** = Confidence Interval, **GA=**gestational age

V. Discussion

In this study, the prevalence of AKI among asphyxiated term neonates using creatinine was 42.9%; this is similar to the prevalence of 43.0% and 47.1% recorded in India by Jayashree *et al* [24] and Gupta *et al* [11] respectively. Both studies used urine output and serum creatinine levels > 90µmol/l at 48 hours in the diagnosis of AKI. In this study however a rise in serum creatinine ≥ 0.3mg/dl (26.4µmol/L) within 48 hours was used to diagnose AKI (Neonatal KDIGO).[25] Martin -Ancel *et al* [26] recorded an AKI prevalence of 42% among term asphyxiated babies; this is similar to the result obtained in this study; however urine output and absolute creatinine values were used to diagnose AKI in that study. Alaro *et al* [27] recorded a lower prevalence of 11.7% in a similar study where AKI was diagnosed using day 2 and 3 creatinine > 133µmol/l. The adduced reason for this lower prevalence could be because of a higher cut off value of serum creatinine (>133 µmol/L) used in the

diagnosis of AKI, furthermore because a relatively smaller sample size was used in that study (60 asphyxiated babies).

In a similar North-American study, a prevalence of 61.0% was reported among asphyxiated neonates using serum creatinine.[9] This high prevalence reported could be attributed to the fact that only severely asphyxiated babies developed AKI in that study and the prevalence recorded was among the severely asphyxiated babies as none of the moderately asphyxiated babies had AKI, as such the value reported would be expectedly higher. It is pertinent to note that it is very difficult to compare the burden of AKI in various studies, as different diagnostic criteria were used in the diagnosis of neonatal AKI.

Gender, social class, birthweight and birth-weight for age were not found to be associated with AKI in asphyxiated neonates in this study. However, a statistically significant association was found between AKI and the grade of asphyxia. This study shows that term neonates with severe asphyxia are seven times more likely to have AKI than those with moderate asphyxia. This is not unexpected as babies with severe asphyxia are more likely to suffer profound renal injury.[28] Subjects with severe perinatal asphyxia have a more progressive damage arising from marked hypoxia and oxidative stress. The renal parenchyma cells have a limited capacity for anaerobic respiration and a high susceptibility for reperfusion injury, which correlates strongly with the severity of asphyxia.[29]A similar finding was reported in a study done in the Democratic Republic of Congo, where 54% of severely asphyxiated neonates had AKI compared to 31.4% of the moderately asphyxiated subjects.[30]

A study in India conducted among 95 asphyxiated neonates found that factors such as gender, gestational age and birth weight did not differ significantly among the different stages of AKI. Furthermore, there was also no correlation between the severity of HIE and the grade of AKI in that study.[31] The finding in that study was a clear departure from earlier mentioned patterns where severe asphyxia was found to be significantly associated with AKI in asphyxiated neonates. The reason for this is not clearly understood.

VI. Conclusion

The prevalence of AKI among moderately and severely asphyxiated term neonates in UDUTH Sokoto is high. The grade of asphyxia was found to be significantly associated with AKI as severe asphyxia was a strong association observed in this study.

VII. Recommendation

Prompt evaluation geared towards early diagnosis of AKI in asphyxiated neonates, especially severely asphyxiated neonates to enhance timely institution of management.

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