ORIGINAL ARTICLE

Risk factors for acute kidney injury in newborns hospitalized at Jos University Teaching Hospital

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Abstract

Background: In critically ill newborns, the risk factors for developing Acute Kidney Injury (AKI) vary widely and multifactorial; it involves several potential exposures including nephrotoxic medications, sepsis, hypotension and adverse perinatal events such as asphyxia. We sought to identify the risk factors for AKI, and to determine the relative risks for AKI in sick newborns hospitalized at the Special Care Baby Unit (SCBU) of Jos University Teaching Hospital (JUTH).

Methods: This was a prospective cohort study conducted among 150 sick newborns recruited consecutively at the SCBU of JUTH. Changes in serum creatinines and estimated glomerular filtration rates (eGFR) of the babies were used to identify babies with AKI. Risk factors associated with AKI were identified using Chi-square.

Result: The prevalence of AKI in the study population was 14.7%, sepsis ($0.001^{F)}$ and dehydration (X^2 =15.084; p= 0.001) were found to be significantly associated with AKI. Those with sepsis and dehydration were 5 times each more likely to develop AKI than those without it, and both were statistically significant. Sepsis (RR= 4.9, 95% CI=1.72-13.72), dehydration (RR= 4.7, 95% CI= 2.33-8.63).

Conclusion: Sepsis and dehydration are risk factors associated with development of AKI.

Key words: Risk factors, Acute kidney injury, Newborns, Hospitalized.

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Introduction

Acute kidney injury(AKI) defined as sudden reduction in kidney function, results in the inability of the kidneys to maintain fluid and electrolyte homeostasis.[1] Acute kidney injury occurs in children across all age groups but presents a peak in the neonatal period, with as many as 8% of infants in the neonatal intensive care unit developing AKI.[1] A study by AWAKEN (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) to describe the epidemiology of AKI reported an AKI prevalence of as high as 30% in hospitalized neonates,[2] also a study in Addis Ababa, Ethiopia reported a prevalence of 12.7%.[3]

Potential causes of AKI are mainly related to impaired microcirculation, with consequent focal mismatch between oxygen and nutrient delivery to the nephrons and increased energy demands due to cellular stress.[4] Acute kidney injury based on the etiology may be classified as pre-renal, intrinsic renal, or postrenal.[4,5] Pre-renal AKI is functional response of structurally normal kidneys to hypoperfusion, resulting usually from any process that decreases renal blood flow to the glomeruli. In pre-renal AKI, renal hypoperfusion leads to a decreased GFR without damage to the renal parenchyma.[6] Intrinsic renal AKI involves structural damage to the renal parenchyma that may result from failure to reverse any cause of prerenal AKI or direct toxicity to the tubules from medications and other nephrotoxins, interstitial and glomerular diseases, or failure to relieve urinary tract obstruction.[7] Postrenal AKI is caused by obstruction to urinary flow e.g. in posterior urethral valve. Following acute obstruction to the urinary flow, there is an increase in intra-tubular pressure and thus decreases the GFR.[4]

Prevalence of AKI in sick neonates is high as reported by several studies, and it is associated with increased risk of morbidity and mortality.[4,8] Furthermore, AKI in the neonatal period has also been reported as one risk factor for developing chronic kidney disease (CKD) and hypertension in later years.[9] If the risk factors for AKI in newborns are identified and prevented, then it may be possible to reduce the high prevalence of AKI in newborns and the attendant unfavorable outcomes associated with it. There are few studies in Nigeria that have assessed renal function in the sick newborns, and no such study in North central Nigeria where Jos University Teaching Hospital is located.

This study thus aimed at identifying the risk factors for acute kidney injury in newborns, and determining the relative risk for AKI in all the babies admitted into the Special Care Baby Unit (SCBU) of the Jos University Teaching Hospital (JUTH).

METHODOLOGY

Study Area

This study was conducted between November 2018 and April 2019 at the SCBU of Jos University Teaching Hospital, Jos, Plateau state, Nigeria. Being a tertiary health facility, the hospital serves as a referral centre for

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patients from neighbouring states of Kaduna, Nasarawa and Bauchi, and even from other secondary and tertiary health facilities within the state. The SCBU has a bed capacity of 40. The average number of admissions per month was 50 (32-60). Basic facilities for newborn care such as intravenous fluid therapy, naso-gastric feeding, and respiratory support like AMBU bagging, oxygen therapy are available. The SCBU is equipped with 8 functional incubators, phototherapy units, two radiant warmers, bubble continuous positive airway pressure (BCPAP) and a ventilator. The chemical pathology laboratory is located in the laboratory complex, a five-minute walking distance from the SCBU.

Study Design

This was a prospective cohort study.

Ethical Consideration

Ethical approval was obtained from the Jos University Teaching Hospital research and ethical committee with reference number JUTH/DCS/ADM/127/XXVII/768. A written informed consent was obtained from the parents/ caregivers of the neonates before recruitment.

Inclusion Criteria

Sick neonates admitted into the SCBU between 0 and 72hours of life, both term and preterm, whose parents/ care givers consented to the study.

Exclusion Criteria

Babies that died between 72hours and day 7 of life as well as babies admitted after 72hours of life. Babies with congenital renal anomalies.

Sample Size

The minimum sample size was determined using the Beneth- Fischer's formula at alpha level of 0.05 and power of 95%.[10] Therefore, the minimum sample size was 150.

Sampling Technique

Babies admitted into the SCBU who fulfilled the inclusion criteria were recruited consecutively till the sample size was completed.

Data Collection

A pilot study was done using 10% of the estimated sample size in the SCBU of JUTH prior to data collection and findings used to revise the study tools. No major changes were made to the research materials following the pilot study. Data was collected by the researchers, 2 research assistants and other resident doctors on call when babies were admitted at unusual hours e.g. midnight.

Personal data, medical and social information, including gender, age, estimated gestational age, birth weight, contact phone number and the socioeconomic levels of both parents were obtained using the pretested investigator administered questionnaire. The socio-economic status was determined using the system suggested by Olusanya *et al*.[11]

Information on the diagnoses (determined using appropriate diagnostic criteria) were captured in the questionnaire. Infant weight was measured using calibrated WAYMASTER^{R}(England) bassinet weighing scale with precision of 0.05kg. The scale was zeroed before each measurement, and reading was taken with the infant unclothed. Recumbent length of the baby was measured using a calibrated infantometer with a precision of 0.1cm. With the assistance of a trained research assistant, each infant was positioned supine with the head firmly against a fixed headboard, knees gently extended, and feet placed flat against the movable footboard, then the length recorded. The head circumference was determined using a flexible non-stretchable tape rule in cm. The gestational age was determined by the mother's last menstrual period or early obstetric ultrasound scan (done before 20weeks of gestation), but where these could not be obtained, the new Ballard score was used to determine the gestational age. All the babies were classified based on their weight for gestational age into; appropriate for gestational age (AGA), small for gestational age (SGA) and large for gestational age (LGA) using the Lubchenco charts. The birth weight was used for babies seen within 24hours, beyond that the admission weight which was believed not to be too different from birth weight was used.

Two milliliters of venous blood sample was collected from each subject by phlebotomy, using standard aseptic procedure (from the antecubital fossa, dorsum of the hand or foot). Serum creatinine (SCr) assay was done at 72hours of life, and then at age 7 days for each baby and rise in creatinine was determined to identify babies with AKI. Serum Creatinine was estimated by the modified kinetic Jaffe reaction**.** The estimated eGFR for each subject was calculated from the serum creatinine value using the Schwartz formular at 72hours of life and then at age 7days. AKI was defined as an increase in serum creatinine of above 150% from previous trough value, or fall in eGFR by 25% of the previous baseline value,[13,14] or single abnormally high value greater than132.6µmol/L regardless of age and urine output.[15]

Analysis of Data

All the data generated were entered into a computer and analyzed using epi info version 3.5.3 statistical software. A spread sheet was prepared on the software programmed for the entry of data obtained from each participant while analysis of data was performed on the

EPI info dashboard. Quantitative variables such as birth weight, length, head circumference were expressed using mean, standard deviation and range, while qualitative variables were summarized using frequency and percentages. Comparison of two means was done using the student's t-test. Chi square test was used to determine the relationship between qualitative variables. A 95% confidence interval was used in this study and a p-value of < 0.05 was considered statistically significant.

Results

A total of 150 neonates were recruited to participate in the study, and all completed the study. Table I shows the demographic characteristics of study subjects. There were 84 (56%) male and 66 (44%) female subjects, with a male to female ratio of 1.3:1. Forty-four (29.3%) were preterm, 104 (69.3%) were term, while 2 (1.3%) were post term babies. Participants were largely between ages 24-48hours on recruitment for the study. The two most predominant ethnic groups were Berom 34 (22.7%) and Hausa 21 (14.0%).

Among the subjects, 55 (36.7%) were from upper social class families, while 48 (32.0%) and 47(31.3%) were from the middle and lower social classes respectively. Majority of the babies (62.0%) were born outside the facility and vaginally 112(74.7%).

The socio-demographic characteristics did not differ significantly between the male and female subjects.

Table II shows the SCr and GFR of subjects with AKI at 72 hours and on day7. Highlighted on the table are the percentage rises in SCr and falls in GFR between 72 hours and day 7. The rise in SCr ranged between 155% and 800%, while fall in GFR ranged between 33.6% and 87.5%. Of the 150 babies studied. Twenty two babies (14.7%) fulfilled the criteria for AKI diagnosis**;** defined as an increase in serum creatinine above 150% from previous trough value, or fall in eGFR by 25% of the previous value. (Table III)

Table I: Socio-demographic characteristics of the study Subjects

Characteristic	Male n=84	Female n=66	Total n= 150	χ^2	p-value
Age on admission					
<24hours	18 (52.9)	16 (47.1)	34 (22.7)		
24-48hours	36 (54.5.5)	30 (45.5)	66 (44.0)		
49-72hours	30(60)	20(40)	50(33.3)	0.295	0.86
Ethnicity					
Hausa	6(28.6)	15(22.7)	21(14.0)		
Yoruba	7(58.3)	5(41.7)	12(8.0)		
Igbo	7(53.8)	6(46.2)	13(8.7)		
Berom	20(58.8)	14(21.2)	34(22.7)		
Others	44(62.9)	26(37.1)	70(46.7)	7.909	0.095
Place of Birth					
Inborn	30(52.6)	27(47.4)	57(38)		
Outborn	54(58.1)	39(41.9)	93(62)	0.354	0.55
Gestational age					
Preterm	22(50.0)	22(50.0)	44(29.3)		
Term	60(57.7)	44(42.3)	104(69.3)		
Post term	2(100.0)	0(0.0)	2(1.3)		0.324[F]
Mode of Delivery					
Vaginal Delivery	60	52	112		
Caesarean Section	24	14	38	1.04	0.308
Social Class					
Upper	30(54.5)	25(45.5)	55(36.7)		
Middle	29(60.4)	19(39.6)	48(32.0)		
Lower	25(53.2)	22(46.8)	47(31.3)	0.578	0.75

[F]=*Fishers Exact P-value*

Table II: Changes in Serum Creatinine and Glomerular Filtration Rates(GFR) in Subjects with AKI.

S/No	Scr (μmol/L)		Rise in Scr(%)	GFR (ml/min/1.73m2)		Fall in GFR (%)
	At 72hrs	On Day 7		At 72hrs	On Day 7	
1	100.0	155.0	155.0	12.8	8.5	33.6
2	105.0	163.0	155.2	18.6	12.0	35.5
3	95.0	162.0	170.5	12.9	7.5	41.8
4	100.0	183.0	183.0	12.8	7.0	45.3
5	80.0	149.0	186.2	23.5	12.6	46.4
6	110.0	204.6	186.0	11.7	6.3	46.2
7	98.0	185.0	188.7	21.3	11.2	47.4
8	128.0	253.0	197.6	15.8	8.0	49.4
9	90.0	193.0	214.4	22.1	9.2	58.4
10	99.5	239.0	240.2	19.6	8.1	58.7
11	90.0	241.0	267.8	18.0	6.6	63.3
12	95.3	264.0	277.0	20.0	7.3	63.5
13	95.0	271.7	286.0	13.0	4.5	65.4
14	105.0	321.0	305.7	18.9	6.2	67.2
15	140.0	459.2	328.0	13.7	4.2	69.3
16	85.0	323.0	380.0	23.9	6.3	73.6
17	108.0	432.0	400.0	18.4	4.7	74.5
18	120.0	546.0	455.0	17.2	3.8	77.9
19	130.0	681.0	523.8	15.0	2.9	80.7
20	120.0	644	536.7	16.2	3.0	81.5
21	120.0	762.0	635.0	15.9	2.5	84.4
22	130.0	1040.0	800.0	15.9	2.0	87.4

SCr: Serum Creatinine .GFR: Glomerular Filtration Rate

Table III: Prevalence of Acute Kidney Injury in study population

	AKI	
	Frequency	Percentage
AKI	22	14.7
No AKI	128	85.3
Total	150	100.0

The aetiologic factors for AKI are outlined in Table IV. In the study population, sepsis (0.001[F]) and dehydration (X^2 =15.084; p= 0.001) were found to be significantly associated with AKI, those with sepsis and dehydration were also 5 times each more likely to develop AKI than those without them, and both were statistically significant. Sepsis (RR= 4.9, 95% CI= 1.72-13.72), dehydration (RR= 4.7, 95% CI= 2.33-8.63).

The prevalence of AKI among the study subjects in relation to socio-demographic characteristics and some selected factors is as shown in Table V. Of the 22 subjects with AKI, 8 (36.4.0%) were born in the facility, while 14 (63.6%) were born outside the facility. There was no statistically significant association between place of birth and prevalence of AKI. There were 12 (14.3%) males with AKI, and 10 (15.2%) females, giving a male to female ratio of 1.2:1. There was no statistically significant association between gender and prevalence of AKI.

AKI was not found to be significantly associated with social class, gestational age, birth weight, and weight for gestational age or mode of delivery (Table V).

The diagnoses of the aetiologic factors were made based on the following. Sepsis- Suspected (based on

Table IV: AKI and Aetiology Using Chi-square, and Relative Risk of Factors Associated with AKI in study population

Aetiology	AKI		χ^2	RR	95%CI	p-value
	Yes	No				
Sepsis						
Yes	18(24.3)	56(75.7)				
No	4(5.3)	72(94.7)		4.875	1.72-13.72	0.001[F]
Asphyxia						
Yes	6(18.2)	27(81.8)				
No	16(13.7)	101(86.3)	0.418	1.330	0.57-3.13	0.52
Hyperbilirubinaemia						
Yes	1(4.3)	22(95.7)				
No	21(16.5)	106(83.5)		0.263	0.04-1.86	>0.200[F]
Dehydration						
Yes	6(54.5)	5(45.5)				
No	16(11.5)	123(88.5)	15.084	4.739	2.33-8.63	0.001
Omphalocelle						
Yes	1(20.0)	4(80.0)				
No	21(14.5)	124(85.5)		1.381	0.23-8.33	0.55[F]
Necrotizing enterocolitis(NEC)						
Yes	1(20.0)	4(80.0)				
No	21(14.5)	124(85.5)		1.381	0.23-8.33	0.55[F]
Meconium aspiration sydrome						
Yes	1(20.0)	4(80.0)				
No	21(14.5)	124(85.5)		1.381	0.23-8.33	0.55[F]

[F]=*Fishers Exact P-value. Highlighted p-values were significant. RR= Relative Risk*

clinical features) or proven infection (positive culture of body fluids like blood, Cerebrospinal fluid) plus at least one of; abnormal body temperature (> 38.5°C *or* < *36.0°C*) or abnormal leukocyte count; <4,000/mm^2 or >30,000/mm^2, or >10% immature cells.[16] Asphyxia- Apgar scores of 6 or below at 5 minutes and beyond, with neurologic signs like seizures, abnormal muscle tone, coma.[17]

Hyperbilirubinaemia- Total serum bilirubin above physiologic jaundice ≥13mg/dL.[18]

Dehydration- Elevated blood urea nitrogen with one or more of; depressed fontanelle, loss of skin turgor, sunken eye, other features of dehydration.

Necrotizing Enterocolitis- Presence of bloody stool, abdominal distension, feeding intolerance, plain abdominal radiograph showing pneumatosis intestinalis.[19]

Meconium Aspiration Syndrome- Respiratory distress in a newborn born through meconium-stained amniotic fluid, with no other apparent cause for the distress.[20]

Discussion

AKI was found in 14.7% of newborns studied in our SCBU, with sepsis the most common factor associated with development of AKI, present in as much as 82% of babies with AKI. This finding is consistent with findings in most studies around the world, where sepsis was a major risk factor for developing AKI. In a study by Hossein *et al*[12] sepsis was the most common predisposing factor for AKI, as high as 77.5% comparable to this study. The likely reason for high prevalence of sepsis in babies in this study and the study by Hossein is the large number of outborn babies in the study populations, 62.0 % and 49.0 % respectively. Outborn deliveries include home deliveries, deliveries in prayer houses, and deliveries in vehicles among others; it is therefore likely that these deliveries occurred in septic circumstances which predisposed the newborns to infection. Unsafe and unclean environments, use of unsterilized instruments, limited skilled manpower and inadequate facilities are possible predisposing and risk factors for sepsis in outborn deliveries.[22] Similar pattern of etiologies were

Table V: Associations between Socio-demographic Determinates, other factors and prevalence Acute Kidney Injury in the study population.

Factor	AKI		χ^2	p-value
	Yes	No		
Place of birth				
Inborn	8(14.0)	49(86.0)		
Outborn	14(15.1)	79(84.9)	0.029	0.86
Gender				
Male	12(14.3)	72(85.7)		
Female	10(15.2)	56(84.8)	0.022	0.88
Social Class				
Upper	9(16.4)	46(83.6)		
Middle	6(12.5)	42(87.5)		
Lower	7(14.9)	40(85.1)	0.578	0.75
Gestational Age				
Preterm	5(11.3)	39(88.6)		
Term	16(15.4)	88(84.6)		
Post term	1(50.0)	1(50.0)		0.15[F]
Weight For Gestational Age				
AGA	18(14.3)	108(85.7)		
SGA	3(21.4)	11(78.6)		
LGA	1(10.0)	9(90.0)		>0.99[F]
Birth weight				
Low	8(15.7)	43(84.3)		
Normal	13(14.4)	77(85.6)		
Macrosomia	1(11.1)	8(88.9)		0.84[F]
Delivery Mode				
Vaginal	18(16.1)	94(83.9)		
Ceaserean Section	4(10.5)	34(89.5)		0.59[F]

[F]=*Fishers Exact P-value Outborn: Babies born outside JUTH.*

also reported in similar studies in developing countries by Vachvanichsanong and Afia *et al*; sepsis was the leading cause.[23,24] Babies in our study with sepsis were 5 times more likely to develop AKI than those without sepsis. Babies with sepsis develop AKI from hypotension and direct effect on renal microvasculature.[25] Other mechanisms of AKI in sepsis include inflammation, coagulation and obstruction of tubules with necrotic cells.[26,27]

Also identified to be significantly associated with AKI in our study was dehydration. Lactation failure has been reported as one major cause of dehydration in breastfed newborns,[28,29] which may be the case in most babies that presented with severe dehydration in this study. Other factors associated with feeding problems in newborns which may have contributed to dehydration in this study includes shorter postpartum hospital stay, inconsistent follow-up breast-feeding support, lower socioeconomic status, and general lack of health care support.[27] All but one of the babies that developed AKI from dehydration in this study were outborn, implying that they either received a suboptimal or no antenatal care where breastfeeding and early infant care was usually taught. In several other studies, though not statistically significant, dehydration has been mentioned as an important factor associated with AKI, especially in developing countries.[23,30] The relative risk (RR) of dehydration in this study was 4.7, hence subjects with dehydration were about 5 times more likely to develop AKI than those without dehydration. Dehydration causes AKI by reducing effective extracellular volume, leading to decreased renal blood flow and GFR from renal vasoconstriction mediated by adrenergic activity.[6] Prolonged hypovolaemia and decreased renal hypoperfusion from dehydration may then result in intrinsic AKI from ischemic insult to the tubular cells.[31,32]

We found asphyxia to be a statistically insignificant third leading cause of AKI in our hospitalized sick newborns, contrary to the pattern in many other studies. A study in Ethiopia by Nida *et al*[3] identified perinatal asphyxia as the leading cause of AKI in newborns, this is also consistent with the findings by Agras *et al.*[33] A study in Jordan by Abu-Haweleh *et al* reported asphyxia as the major cause of AKI in neonates, followed by sepsis.[34] The reason for asphyxia not being a significant risk factor for AKI in this study was not clear, but may be due to the criteria used to diagnose birth asphyxia; APGAR scores though a globally used diagnostic tool for birth asphyxia, has low sensitivity and positive predictive value.[17] hence the asphyxia in these babies may not correlate well with the development of AKI as in other studies where other more reliable methods such as arterial blood gas and pH were used, also, improved post-resuscitation-care given to the babies with prompt resolution of their symptom. A similar finding was also reported by Kungwani *et al*[35] in India. In a study by El-Badawy *et al*,[5] male sex and necrotizing enterocolitis were significant risk factors for developing AKI, though not statically significant, sepsis was the most common risk factor. The small sample size and single-center data of the study reduced the generalizability and reliability of the study.

In this study, gender, gestational age, birth weight, place of birth, maturity, necrotizing enterocolitis, and meconium aspiration syndrome were not found to be significant risk factors for AKI in sick neonates, no clear reason for this.

Conclusion

Sepsis and dehydration are significantly associated with occurrence of AKI in the newborn babies. Optimal antenatal and immediate postnatal care and education are recommended for all pregnant women to stem the tides of early onset neonatal infections and lactation failure which have been shown to contribute significantly to the development of AKI in these newborns

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