Journal of Pediatric Academy

Original Article

Year: 2025 Volume: 6 Issue: 1
Doi: 10.4274/jpea.2025.364
J Pediatr Acad 2025; 6: 15-19

Acute Kidney Injury As A Consequence of Perinatal Asphyxia

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Article Information

Article Type: Original Articles
Article Group: Pediatric Nephrology

Received: 04.11.2024
Accepted: 05.03.2025
Epub: 14.03.2025
Available Online: 26.03.2025

Cite this article as: *Rahman O, Rahman M, Adnan MA, Hye A. Acute kidney injury as a consequence of perinatal asphyxia. J Pediatr Acad. 2025; 6: 15-19*

Abstract

Perinatal asphyxia (PNA) results in multiorgan damage including the kidney. The severity of kidney damage is related to the extent of central nervous system damage. This study aimed to determine the prevalence of acute kidney injury (AKI) in neonates with PNA and its association with hypoxic ischemic encephalopathy (HIE) staging. This cross-sectional study was conducted in the neonatal intensive care unit of the Institute of Child and Mother Health, Dhaka, from July 2020 to June 2021. A total of 100 neonates with PNA were included in this study. After careful history taking, examination, and appropriate investigations, HIE staging was done in each subject using the Sarnat and Sarnat method. Data were analyzed by statistical package for the social sciences, version 23. In this study, 45 (45.0%) neonates belonged to the postnatal age group ≤24 hours, and male patients were predominant (57.0%). Out of 100 neonates, 89.0% had HIE stage II and 11.0% had stage III. Among stage II HIE neonates, 9 (10.1%) had AKI and 80 (89.9%) did not have AKI. Among stage III HIE neonates, 5 (45.5%) had AKI and 6 (54.5%) did not have AKI. The difference was statistically significant ($p<0.05$). When HIE stage was higher in PNA patients, there was a higher possibility of developing AKI. Renal function alterations correlated with HIE severity. Therefore, AKI should be evaluated and properly managed among neonates with PNA.

Keywords: Acute kidney injury, hypoxic ischemic encephalopathy, perinatal asphyxia

Introduction

Perinatal asphyxia (PNA), an important cause of neonatal morbidity and mortality, has been a global concern. Its incidence ranges from 1 to 10 per 1,000 live births (McGuire)[1]. Approximately 90% of asphyxial events occur during the antepartum or intrapartum period as a result of placental insufficiency with an inability to provide oxygen and remove CO_2 and hydrogen ions from the fetus. The remaining 10% are postpartum, usually secondary to

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pulmonary, cardiovascular, or neurologic insufficiency (Hansen and Soul[2]).

Rena hypoperfusion as a consequence of PNA acts as pre-renal acute kidney injury (AKI) trigger. Abundance of mitochondria in tubular cells makes the kidney highly oxygen dependent as well as susceptible to oxidative stress. Generation of various reactive oxygen species (e.g., hydroxyl radical, peroxynitrite, hyperchlorous acid) and depletion of some antioxidants (superoxide dismutase, catalase, and glutathione reductase) adversely affect renal tissue, leading to AKI (Gyurászová et al.[3]). The incidence of neonatal AKI ranges from 8% to 20%. The mortality in neonates with AKI is very high as well (Srivastava and Bagga[4].)

Highlights

- Perinatal asphyxia (PNA) is an established cause of multiorgan damage,
- Kidney involvement in PNA ensues significant morbidity and mortality,
- Our study was aimed at determining the percentage of acute kidney injury in PNA, as well as to investigate its association with various stages of hypoxic ischemic encephalopathy.

The present study is aimed to determine the percentage of AKI in PNA and its association with hypoxic ischemic encephalopathy (HIE) staging.

Material and Method

This was a cross-sectional study carried out at neonatal intensive care unit (NICU), Institute of Child and Mother Health (ICMH), and Dhaka Medical College Hospital, Dhaka. The duration of the study was one year, from July 2020 to June 2021. Both in-born and out-born neonates diagnosed with PNA and HIE stage II or III, born at 37-42 weeks of gestation and admitted to the NICU within 72 hours of life, were enrolled. Neonates with any congenital anomaly, PNA, and or antenatal diagnosis of any kidney disease were excluded.

As it was a cross-sectional study, the sample size was calculated using the following formula.

$$n=z^2p(1-p)/d^2$$

$$= \frac{(1.96)^2 x\ 0.12(1-0.12)}{(0.05)^2}$$

$$= \frac{3.8416x0.12x0.88}{0.0025}$$

$$= 162$$

[Where n: sample size, z: 1.96 (standard normal deviate), p means prevalence: 0.12 (Alaro et al.[5]). The degree of accuracy or precision level is d which is considered at 5%] .

By using the above formula, the expected sample was 162, but due to time limitations, 100 subjects were enrolled.

Newborns with PNA admitted to the NICU of ICMH were included in this study irrespective of their gender, race, and ethnic group. After enrollment, a detailed history was taken and a thorough clinical examination was performed. HIE staging was performed on these patients by Modified Sarnat and Sarnat staging (Gomella et al.[6]).

AKI was diagnosed using the kidney disease: improving global outcomes criteria. With all aseptic precautions, a blood sample (3 mL of venous blood) was collected using a disposable syringe from each neonate. The collected blood sample was taken into a sterile test tube and labeled with the identification number, date, and sent to the laboratory of ICMH for investigation. For the complete blood count, a collected blood sample was taken in an ethylenediaminetetraacetic acid sterile tube, and the test was performed using the Sysmex XN-550 machine made in India. Capillary blood glucose was measured by a glucometer from a heel prick, and serum electrolytes were analyzed using the EasyLyte PLUS Electrolyte analyzer made in India. Blood urea and serum creatinine measurements were conducted with the HumanStar 600 autoanalyser machine made in India.

The protocol was submitted and approval was obtained from the Institutional Review Board (IRB) (respective ethics committee) of the ICMH, Dhaka, Bangladesh (approval no.: ICMH/IRB-07SEP2020/17). Informed written consent was obtained before starting the interview. This research activity would not cause any harm to patients.

Statistical Analysis

Checked and cleaned data were analyzed using statistical package for the social sciences version 23. The chi-square test and Fisher's were used for qualitative variables. Unpaired Student's t-test was used for quantitative variables. The p-value <0.05 was considered significant.

Results

The majority of the neonates (45%) belonged to age group ≤24 hours, while 26.0% belonged to age group 25-48 hours and 29.0% belonged to age group 49-72 hours (**Figure 1**). The study found a male predominance (57%) over females (43%) (**Figure 2**). The majority of the mothers (73%) had irregular antenatal visits. Regarding risk factors, 30% had premature rupture of membrane (PROM), 18% had prolonged/obstructed labor, 11% had hypertension (HTN), 8% had diabetes

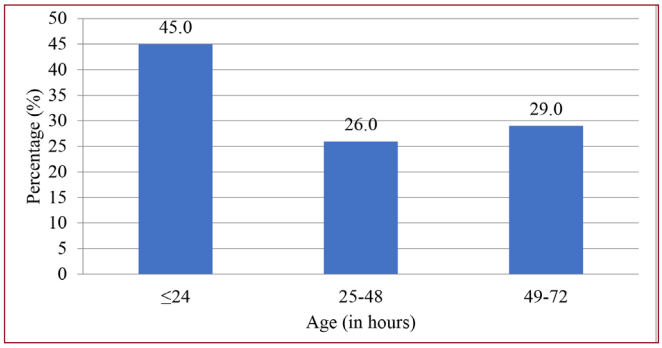

Figure 1. Bar diagram showing age distribution of the neonates (n=100)

mellitus (DM). Most of the mothers (59.0%) had normal vaginal delivery, and 53.0% of the mothers had home delivery (**Table 1**).

About 78.0% of patients had a lethargic appearance; almost 67.0% of patients showed pale color; the majority (67.0%) of patients had a capillary refill time of less than 3 seconds. The majority (64.0%) had a moderately low score (4-6) at 1 minute, and (59.0%) had a moderately low score (4-6) at 5 minutes (**Table 2**).

The majority of cases (89.0%) were classified as HIE stage II, while 11% were classified as HIE stage III (**Figure 3**). Out of 100 cases of PNA, 86 (86%) were found without AKI, and the remaining 14 (14%) had AKI (**Figure 4**). Among the 89 cases with HIE stage II, 9 cases (10.1%) developed AKI, while AKI developed in 5 cases (45.5%) out of 11 HIE stage II cases (**Table 3**). This finding was statistically significant. Differences in serum creatinine and blood urea levels were statistically significant between AKI and without AKI groups, while the differences between blood cell counts, C-reactive protein, serum electrolytes, and calcium levels were not statistically significant (**Table 4**).

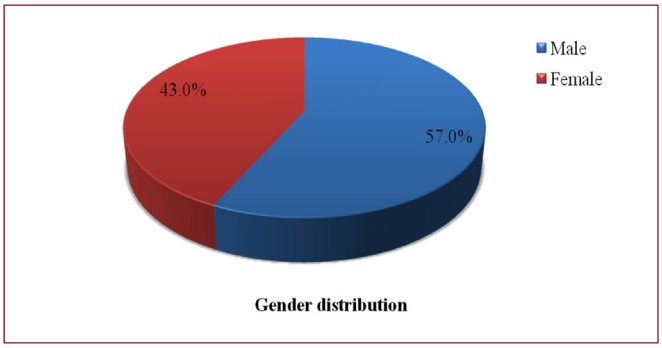

Figure 2. Pie chart showing gender distribution of the study neonates (n=100)

Table 1.
Factors influencing neonatal outcome (n=100)

Related factors	Frequency	Percentage
Antenatal visit		
Regular	12	12.0
Irregular	73	73.0
None	15	15.0
Risk factors		
PROM	30	30.0
Prolong/obstructed labor	18	18.0
HTN	11	11.0
DM	8	8.0
Bronchial asthma	3	3.0
PV bleeding	5	5.0
Meconium-stained liquor	3	3.0
None	22	22.0
Gestation		
Single	100	100.0
Twin	0	0.0
Mode of delivery		
NVD	59	59.0
LUCS	41	41.0
Place of delivery		
Home	53	53.0
Hospital	32	32.0
Clinic	15	15.0

PROM; Premature rupture of membrane, HTN; Hypertension, DM; Diabetes mellitus, PV; Per vaginal, NVD; Normal vaginal delivery, LUCS; Lower uterine cesarean section

Discussion

The pathology of PNA lies in defective blood gas exchange and eventual progression to hypoxemia, along with hypercapnia. It also causes HIE, a significant etiology of neonatal death.

Table 2.
Clinical profile of study neonates (n=100)

Presenting signs	Frequency	Percentage
Appearance		
Lethergic	78	78.0
Active/alert	22	22.0
Colour		
Pink	25	25.0
Pale	67	67.0
Cyanosis	8	8.0
Capillary refill time		
<3 second	67	67.0
≥3 second	33	33.0
APGAR score at 1 minute		
Normal 7-10 score	36	36.0
Moderately depressed 4-6 score	64	64.0
APGAR score at 5 minute		
Normal 7-10 score	41	41.0
Moderately depressed 4-6 score	59	59.0

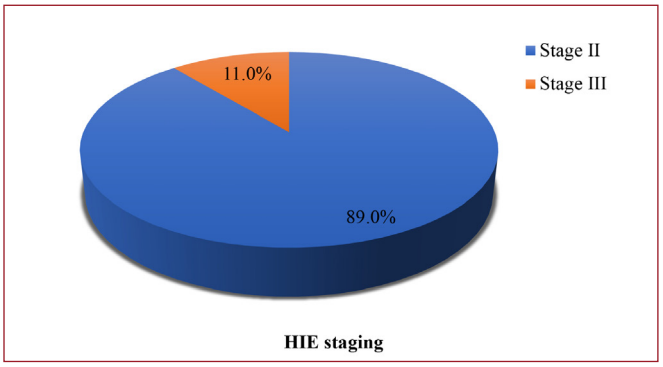

Figure 3. Pie chart showing distribution of cases according to HIE staging (n=100)
HIE; Hypoxic ischemic encephalopathy

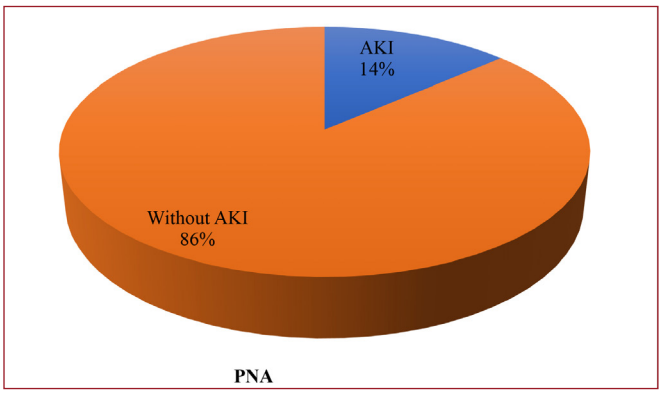

Figure 4. Pie chart showing AKI and without AKI in PNA (n=100)
PNA; Perinatal asphyxia, AKI; Acute kidney injury

Table 3.
Association of HIE staging of AKI and without AKI neonates (n=100)

HIE staging	AKI (n=14)		Without AKI (n=86)		p-value
	n	%	n	%	
Stage II (n=89)	9	10.1	80	89.9	0.001*
Stage III (11)	5	45.5	6	54.5	

*p-value <0.05 was considered as significant, HIE; Hypoxic ischemic encephalopathy, AKI; Acute kidney injury

Table 4.
Laboratory parameters of the study neonates (n=100)

Investigations	AKI (n=14)		Without AKI (n=86)		p-value
	mean	± SD	mean	± SD	
CBC					
Hb% (gm/dL)	18.82	±1.75	17.73	±2.62	0.136
TC-WBC (mm^3)	16710.62	±8941.70	17962.71	±23607.21	0.845
CRP (mg/dL)	33.95	±18.71	26.77	±17.42	0.160
Serum calcium (mg/dL)	9.17	±0.12	8.97	±1.11	0.504
Na (mmol/L)	142.31	±6.53	140.17	±6.01	0.225
K (mmol/L)	6.03	±2.17	5.52	±0.57	0.066
Cl (mmol/L)	106.32	±7.01	108.17	±3.95	0.154
Serum creatinine (mg/dL)	1.67	±0.29	0.85	±0.57	0.001*
Blood urea (mg/dL)	37.87	±13.68	27.53	±9.35	0.001*

Results were expressed as mean ± standard deviation. An unpaired Student's t-test was done as a test of significance.
*p-value <0.05 was considered as significant, AKI; Acute kidney injury, CBC; Complete blood count, Hb; Hemoglobin, TC-WBC; Total count of white blood cells, CRP; C-reactive protein, Na; Sodium, K; Potassium, Cl; Chloride, SD; Standard deviation

The disease process adversely affects various organs, notably the kidneys. A thorough and optimized kidney function evaluation is warranted in these patients (Gopal[7]).

The present study observed 45.0% of neonates aged ≤24 hours, 26.0% aged 25-48 hours and 29.0% beyond 48 hours. Medani et al.[8] in their study reported majority (58.8%) of neonates <7 days of age followed by 36.5% between 8-15 days and 4.7% between 16-28 days.

The present study showed that the majority of neonates were male (57.0%), while the remaining 43.0% were female. Phuljhele et al.[9] studied 241 (58.1%) males and 174 (41.9%) females. Shrestha et al.[10] observed a 1.45/1 male-female ratio in their study.

In the present study, the majority (73.0%) of mothers had irregular antenatal visits. Regarding risk factors, the majority (30%) had PROM; 18.0% had prolonged/obstructed labour; 11.0% had HTN; 8.0% had DM. Alaro et al.[5] observed nearly all mothers (90%) received ANC visit. Gopal[7] observed meconium stained amniotic fluid with prolonged labour as leading pathology (40%) of PNA. Medani et al.[8] reported about two thirds (67.3%) of neonates with PNA and AKI were born to mothers with due antenatal care (ANC) and the remaining one third (32.7%) were devoid of ANC.

In this study, the majority of participants (59, 59.0%) had normal vaginal delivery. More than half (53.0% of) patients had home delivery. Medani et al.[8] reported vaginal delivery (either normally or assisted) as modes of birth in 72.9% of the cases. Eighteen (39.2%) neonates were born at home and 28 (60.8%) were born at clinics.

The current study, showed that the majority (64.0%) had moderately low scores (4-6 scores at 1 minute) and (59.0%) had moderately low scores (4-6 scores at 5 minutes). Shrestha et al.[10] reported in their study that, 71% had an APGAR score of ≤3 at 1 minute, while the APGAR score at 5 minutes was found to be ≤3 in 17% and 4-6 in 77% of cases, respectively. Gopal[7] observed 50 neonates with asphyxia, where 20 (40%) had APGAR score 4-5 at 5 minutes, 18 (36%) had score 6-7, and 12 (24%) had score 0-3.

In the current study, 89.0% cases had HIE stage II and 11.0% cases had HIE stage III. Gopal[7] also found in their study, HIE stage II (25/50) outnumbered stage I (20/50) and stage III (5/50). Phuljhele et al.[9] also reported a majority (242, 58.3%) of HIE-II cases, followed by 121 (29.1%) HIE-III cases and 52 (12.5%) HIE-I cases.

This study found that among 89 patients with HIE stage II, 10.1% developed AKI, while 89.9% did not. Stage III was found in 11 patients, out of which, 45.5% were in the AKI group and 54.5% were in the non-AKI group. The difference was statistically significant (p<0.05) between the two groups. In a study comprising 415 subjects, Phuljhele et al.[9] reported a majority (58.3%) having HIE-II, followed by HIE-III (29.1%) and HIE-I (12.5%). They documented no AKI case from the HIE-I group. Although, 20 (8.2%) subjects having HIE II and 50 (41.3%) subjects having HIE-III developed AKI. Another prospective cohort study in Kenya accounted 15 times higher risk of AKI in HIE III than HIE I (Alaro et al.[5]).

A Tunisian study revealed that among the 15 AKI cases, 10 were in the HIE-II stage according to Sarnat staging (Nouri et al.[11]). In their study, Karlowicz and Adelman[12] found non-oliguric AKI to be predominant

(60%) in asphyxiated newborns, while Jayashree et al.[13] documented oliguric AKI to be predominant in comparable subjects. Few studies also described non-oliguric AKI as being predominant in PNA. Few other studies described non-oliguric AKI as predominant in[14-16].

In this study, higher serum creatinine and blood urea were significantly different between the two groups ($p<0.05$), but there was no difference in electrolyte levels in both groups.

Blood urea and creatinine levels were found to be significantly higher in PNA cases in the study by Chaudhary et al.[17] and by Agrawal et al.[18] respectively. Gopal observed significant differences in the levels of urea and creatinine in asphyxiated neonates with AKI.

We have conducted the study at a limited resource center as well as financial constraint. Traditional creatinine-based criteria were used to diagnose AKI. Many centers are using newer biomarkers, like neutrophil gelatinase-associated lipocalin, cystin C, and kidney injury molecule-1, etc., for early detection of AKI (Canney et al.[19]).

Study Limitations

Due to time constraints, the sample size could not be achieved. Other modern biomarkers of AKI should be checked in conducting further research on this topic. A long-term follow-up is also missing in this study. A further study with a larger sample size in multiple centers, with follow-up, is recommended.

Conclusion

This study showed that 14% of neonates with PNA had developed AKI. Patients with HIE stage II and stage III had developed 10.1% and 45.5% AKI, respectively. A significant association between AKI and HIE staging was observed. When HIE stage was higher, there was a greater likelihood of developing AKI.

Ethics

Ethical Approval: The protocol was submitted and approval was obtained from the Institutional Review Board (IRB) (respective ethics committee) of the ICMH, Dhaka, Bangladesh (approval no.: ICMH/IRB-07SEP2020/17).

Informed Consent: Informed written consent was obtained before starting the interview.

Footnotes

Author Contributions: Rahman O, Adnan MA: Surgical and Medical Practices; Rahman O, Rahman M, Adnan MA: Consept; Rahman O, Rahman M, Adnan MA: Design; Rahman O, Adnan MA, Hye A: Data Collection or Processing; Rahman O, Rahman M, Adnan MA: Analysis or Interpretation; Rahman O, Rahman M, Adnan MA, Hye A: Literature Search; Rahman O, Rahman M, Adnan MA, Hye A: Writing.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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