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Original Research Article

Incidence and outcomes of acute kidney injury in term neonates with hypoxic ischemic encephalopathy: an observational study

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ABSTRACT

Background: Hypoxic ischemic encephalopathy (HIE) is one of the devastating birth related complication. It predisposes the babies to serious outcomes, an important one being acute kidney injury (AKI).
Methods: A prospective crossectional observational study was conducted in Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh between November 2019 and October 2020. 153 term neonates with perinatal asphyxia were enrolled. HIE staging and AKI staging done according to Sarnat and Sarnat classification and KDIGO classification respectively. Outcome in terms of recovery, persistent deranged renal function at discharge or mortality noted.
Results: In our study, incidence of Acute Kidney Injury in Hypoxic Ischemic Encephalopathy neonates was 37.7%. There was around 39-fold increase risk of developing AKI in HIE stage III versus HIE stage I. Mortality rate was found to be 51.6%. Mortality was significantly high in HIE stage III. There was around 5-fold increase risk of mortality in HIE neonates with AKI as compared to HIE neonates without AKI. 50% of the subjects who had AKI and discharged recovered of renal function before discharge and 50% recovered at 1 month follow up. In addition, there was no association found between different stages of HIE with different stages of AKI.
Conclusions: It is better to screen all the birth asphyxia cases for AKI so that they can be detected early and managed accordingly.

Keywords: HIE, AKI, KDIGO

INTRODUCTION

HIE is one of the most serious birth related complication and continues to be a major cause of neonatal mortality and morbidity across the globe. HIE occurs in 1 to 3 per 1000 live births in high-income countries, and up to 20 per 1000 live births in low and middle-income countries.[1] There is no accurate data on number of neonates with HIE in India. Despite intense efforts of reducing HIE through training in neonatal resuscitation it remains a major cause of neonatal mortality and morbidity with obvious influence on their long-term neurodevelopmental outcome. HIE is an abnormal neurobehavioral state consisting of an altered level of consciousness (including hyperalert state) and other signs of brainstem and/ or motor dysfunction due to perinatal asphyxia.[2] Perinatal asphyxia is defined by the WHO as failure to initiate and sustain breathing at birth. The prevalence of perinatal asphyxia in newborns admitted to NICU is 19.8%.[3] Perinatal hypoxia, ischemia and asphyxia refer to the pathophysiologic terms decreased oxygen, blood flow, and gas exchange to the fetus or newborn.[4] Asphyxia can cause multi-organ dysfunction due to redistribution of cardiac output. Perfusion to more vital organs like heart, brain and adrenals is maintained at the expense of kidneys, gut and skin.[5] As a consequence, kidney is one of the frequently injured organs due to perinatal asphyxia. The incidence of renal injury in asphyxiated babies has

been reported between 50-72 per cent in various studies.[5-9] Multi-organ involvement is the hallmark of HIE.[10,11] Involvement of one or more organs present in 82% of the infants having perinatal asphyxia; the central nervous system (CNS) is the most frequently involved (72%). Severe CNS injury always occur with involvement of other organs. In other organ involvement renal system is the most common (42%).[10]

CNS involvement manifests as HIE and renal involvement results in AKI.[12] AKI is common and associated with poorer outcomes in perinatal asphyxia. There is high mortality rate associated with AKI in HIE patients.[13] AKI occur within 24 hours of hypoxic-ischemic events resulting from decreased renal flow and deprived oxygen. If this is prolonged, then it may result in cortical necrosis and irreversible damage.[14] AKI previously known as acute renal failure, is a common and serious medical condition, defined as the abrupt loss of kidney function resulting in retention of nitrogenous waste and inability of kidney to regulate fluid and electrolyte homeostasis.[15] AKI can present with wide range of clinical manifestations from minimal elevation in serum creatinine to anuric renal failure. It can lead to various complications due to accumulation of nitrogenous waste. Widely accepted classification system for AKI are acute dialysis quality initiative's risk, injury, failure, loss, end stage renal disease (RIFLE), AKIN (acute kidney injury network) criteria and KDIGO (kidney disease improving global outcome) classification.

According to KDIGO, AKI is defined as abrupt reduction in the kidney function as either, absolute increase in serum creatinine of more than or equal to 0.3 mg/dl over 48 hrs, or a percentage increase of more than equal to 50% from baseline in last 7 days or reduction in urine output, 6 hrs.[15] Non oliguric type of AKI is more common in HIE.[16-20] Hence, just monitoring urine output does not help in the conclusion of AKI, renal biochemical parameters ought to be observe. Novel biomarkers are in practical use, serum creatinine, the indicator of glomerular filtration rate is still the most frequently used biomarker of renal function despite its known limitations. Since HIE is considered as one of the common and dreadful complication of birth asphyxia we performed this study to determine the incidence of AKI in birth asphyxia and to correlate the AKI with severity of HIE grading of asphyxiated neonates.

Aims and objectives

Aim and objective of current study was to determine the incidence and outcomes of acute kidney injury in term neonates with hypoxic ischemic encephalopathy and find out the association of different stages of HIE with different stages of AKI.

METHODS

This was a prospective cross-sectional observational study conducted in neonatology division, Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh, India during the period from November 2019 to October 2020.

Inclusion criteria

All term babies with perinatal asphyxia as defined by WHO failure to initiate and sustain breathing at birth along with APGAR score <7 at 5 minute of age showing neurological signs admitted in neonatology division of department of pediatrics, Jawaharlal Nehru medical college and hospital Aligarh Muslim University, Aligarh during the study period were enrolled.

Exclusion criteria

Term newborns having CAKUT (congenital anomalies of kidney and urinary tract) detected in ANC anomaly scan or had LUTO (lower urinary tract obstruction) or their mother detected as a case of oligohydramnios in antenatal period were excluded.

Method

Term neonates with perinatal asphyxia admitted within 24 hours of delivery into neonatology division, department of pediatrics, satisfying the inclusion criteria were enrolled after written informed consent obtained from either of the parents having given them clear explanation of the purpose of the study, expected benefits and potential harms. Detailed maternal and neonatal information was collected and recorded in predesigned proforma. Enrolled subjects were graded for HIE according to the Sarnat and Sarnat classification. Serum creatinine and blood urea levels were analysed at birth, 48 hours and day seven of life. Additional blood samples were also withdrawn for venous blood gas (VBG) analysis of enrolled subjects at birth. Blood gas analysis and serum electrolytes included pH, pCO_2, pO_2, Na+, K+, Ca^{2+}, HCO_3, lactate. According to modified KDIGO classification, enrolled subjects were classified for acute kidney injury stages after following their serum creatinine values. Outcomes were noted in terms of either recovery or mortality or persistent deranged renal function at the time of discharge. Subjects with deranged renal function at discharge were followed up at 1 month of age for renal function assessment. Those subjects who had deranged renal function even at 1 month follow up were also planned to followed up at 3 month of age.

Sample size

The sample size was calculated using the formula,

$$n=\frac{4P\,(100-P)}{d^2},$$

where,

n is sample size,

P is anticipated incidence of AKI in birth asphyxia

d is absolute precision which was taken as 99%.

The sample size was found to be 153 on the basis of incidence of AKI in asphyxiated neonates from previous study where the incidence of AKI was 44.21%.[21]

Statistical analysis

The SPSS latest version was used for the entry and analysis of data. Pearson Chi square test was used to analyse all the qualitative variables. Kruskal-Wallis one-way ANOVA test was used to analyse all non-parametric quantitative variables. Repeated measure ANOVA test was used to analyse the variables changing over time. Paired t test was used to analyse two variables. Logistic regression test was used to calculate odds ratio, $p<0.05$ was considered significant.

RESULTS

Out of 153 asphyxiated neonates, 53 (34.6%) were HIE stage I, 22 (14.3%) were HIE stage II and 78 (50.9%) were HIE stage III. Males (n=86; 56.2%) outnumbered females (n=67; 43.7%), with a male:female ratio 1.28:1. Majority of our study population were normal birth weight babies (n=103; 67.3%) and rest were low birth weight (LBW) babies (n=50;32.7%). Mean birth weight of study population was 2.71 kg.

Table 1: Distribution of HIE in study population.

HIE stage	Subjects
	N (%)
Stage I	53 (34.6)
Stage II	22 (14.3)
Stage III	78 (50.9)

Two-third population (n=114; 74.5%) was AGA (appropriate for gestational age) while rest one-third (n=39;25.5%) comprised SGA (small for gestational age). Majority of the babies (n=136; 88.8%) were born between 37-39 (+6 days) weeks of gestation while rest (n=17; 11.1%) babies were born beyond 40 weeks of gestation.

Statistically significant population (n=93; 60.7%) was delivered through lower segment cesarean section (LSCS) and rest (n=60; 39.2%) were delivered through normal vaginal route. MSAF (meconium-stained amniotic fluid) was found in major proportion of our study population (n=129; 84.3%) while rest 24 (15.6%) babies had clear amniotic fluid. Of 153, 88 (57.5%) babies were born to primigravida mothers while 65 (42.4%) were born to multigravida mothers. Majority of the HIE neonate mothers were under 30 years of age. Out of 153 subjects, 12 (7.8%) had mothers under 20, 109 (71.2%) between 20-30 year of age and 32 (20.9%) above 30 years. Of total subjects, 51 (33.4%) had maternal risk factors in which PIH (n=20; 13.1%) was the most common followed by maternal infection (n=18; 11.8%) followed by severe anaemia (n=8; 5.2%) and GDM (n=3; 1.9%). We also had one mother with IHCP (intra hepatic cholestasis of pregnancy) and another with RHD (rheumatic heart disease). Pregnancy induced hypertension (PIH) included a wide range of conditions namely gestational hypertension, severe preeclampsia, non-severe preeclampsia, eclampsia. Maternal infections included maternal sepsis, chorioamnionitis and maternal fever. Maternal fever could be seasonal fever including Plasmodium vivax infection at the time of admission for delivery of the baby.

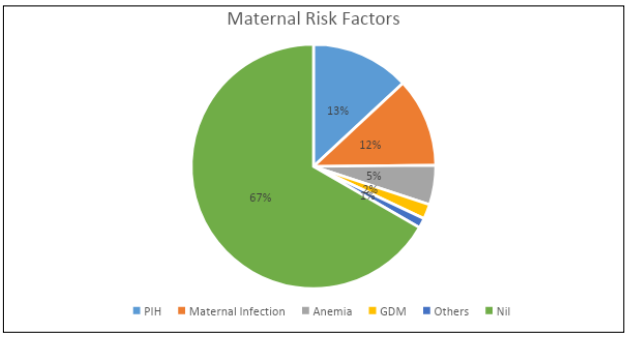

Figure 1: Maternal risk factors associated with HIE neonates.

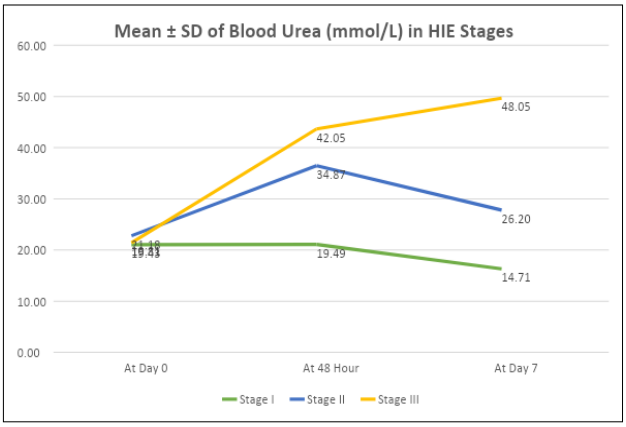

Figure 2: Mean blood urea levels (mmol/l) in HIE stages.

On comparing trend of mean blood urea level in each stages of HIE we found that there was no significance difference at zero hour of life. There was significant difference in levels of advanced stages as compared to HIE stage I at 48 hours of life. Also HIE stage III had persistently high levels mean blood urea (Figure 2). On comparing trend of mean serum creatinine in each stages of HIE we found that there was significant difference in levels of HIE stage III as compared to HIE stage I and II at zero hour, 48 hours and on day 7 of life. HIE stage III subjects had persistently high mean serum creatinine levels (Figure 3). In our study, out of 153 HIE subjects 15

died before completing 48 hours of life therefore AKI staging couldn't be done in those as per KDIGO classification. Of remaining 138 subjects, incidence of acute kidney injury in hypoxic ischemic encephalopathy neonates was found to be 52 (37.7%). Of 52 subjects who had AKI, 34 (65.4%) had AKI stage I, 7 (13.5%) had AKI stage II and 11 (21.1%) had AKI stage III.

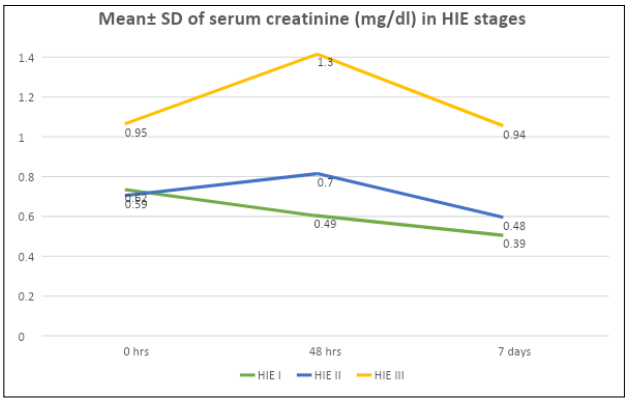

Figure 3: Mean serum creatinine levels (mg/dl) in HIE stages.

There was around 5-fold increase risk of developing AKI in HIE stage II versus HIE stage I (OR=4.90; CI=1.05-22.71; p=0.04) and around 39-fold increase risk of developing AKI in HIE stage III versus HIE stage I (OR=38.59; CI=10.69-139.27; p<0.001) (Table 3). In our study, mortality rate was found to be 51.6%. We found that most of the subjects who had AKI (n=44; 84.6%) were expired while only few of them (n=8; 15.4%) were discharged.

There was around 5-fold increase risk of mortality in asphyxiated neonates with AKI as compared to the subjects without AKI (OR=4.98; 95% CI=2.21-11.21; p<0.001). Four (50%) of the subjects who developed AKI and discharged, recovered before discharge and the rest 4 (50%) recovered at 1-month follow-up. Considering outcome in each stage of HIE in our study, we found almost all subjects of HIE stage I (n=53; 100%) were discharged while 18 (81.8%) of HIE stage II and 3 (3.8%) subjects of HIE stage III were discharged. On the contrary mortality was significant (p<0.001) in advanced stages of HIE (Figure 4). Majority of HIE stage III (n=75; 96.1%) died. In our study we also compared different stages of AKI with the outcome of the subjects which was found to be statistically insignificant. Also the association of different stages of HIE with different stages of AKI was statistically insignificant.

Table 2: Demographic variables in study population.

Variables		Subjects, N (%)
Gender	Male	86 (56.2)
	Female	67 (43.7)
Birth weight	Low birth weight (LBW)	50 (32.7)
	Normal birth weight	103 (67.3)
Growth for gestational age	Small for gestational age (SGA)	039 (25.5)
	Appropriate for gestational age (AGA)	114 (74.5)
Gestational age	Early term (37-39 weeks)	136 (88.9)
	Late term (≥40 weeks)	017 (11.1)
Mode of delivery	Normal vaginal delivery (NVD)	60 (39.2)
	Lower segment cesarean section (LSCS)	93 (60.7)
Amniotic fluid	Meconium stained amniotic fluid (MSAF)	129 (84.3)
	Clear amniotic fluid	024 (15.6)
Gravida	Primigravida	88 (57.5)
	Multigravida	65 (42.4)

DISCUSSION

AKI is common and associated with poorer outcomes in perinatal asphyxia. Kidney is one of the frequently injured organ due to perinatal asphyxia. The incidence of renal injury in asphyxiated babies has been reported between 50-72 per cent in various studies.[5-9] In a prospective case control study conducted in Jodhpur, India incidence of renal failure in asphyxiated neonates was 47.1% which is comparable to our study where we found incidence of AKI among the asphyxiated term neonates was 37.7%. Similarly, multiple studies had been conducted in both low and high income countries but a wide range of AKI incidence in perinatal asphyxia has been noticed depending on the sample size and criteria used for defining AKI.[11,21-25] In our study population, majority of the subjects with HIE stage III developed AKI (n=44; 69.8%) while only 5 (22.7%) subjects of HIE stage II and 3 (5.66%) subjects of HIE stage I developed AKI. Similarly, in studies HIE stage III had higher prevalence of AKI.[13-16] In the study there was a 15-fold increase risk of developing AKI in HIE III versus HIE I, p=0.034. In our study we found

around 5-fold increase risk of developing AKI in HIE stage II versus HIE stage I (OR=4.90; CI=1.05-22.71; p=0.04) and around 39-fold increase risk of developing AKI in HIE stage III versus HIE stage I (OR=38.59; CI=10.69-139.27; p<0.001).[13]

There is high mortality rate reported in perinatal asphyxia associated AKI in previous studies. In an African study it was reported as 71.4%.[13]

Table 3: AKI in each stages of HIE.

AKI	HIE Stage		
	Stage I	Stage II	Stage III
Present	03 (5.7)	05 (22.7)	44 (69.8)
Absent	50 (94.3)	17 (77.3)	19 (30.2)

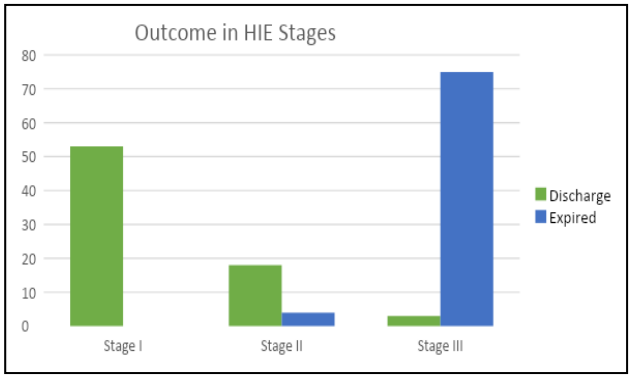

Figure 4: Outcome in HIE stages.

In another study conducted in India it was 27.5%.[16] In our study, mortality rate in perinatal asphyxia associated AKI was 51.6%. We found that most of the expired subjects had AKI 44 (84.6%) while only 8 (15.4%) discharged subjects had AKI. There was significantly (p<0.001) high incidence of AKI in expired subjects. There was around 5-fold increase risk of mortality in neonates who developed AKI as compared to neonates who didn't develop AKI (OR=4.98; 95% CI=2.21-11.21; p<0.001). Considering outcome in each stage of HIE in our study, we found almost all 53 (100%) subjects of HIE stage I were discharged while 18 (81.8%) of HIE stage II and only 3 (3.8%) subjects of HIE stage III were discharged. On the contrary mortality was significant (p<0.001) in advanced stages of HIE. Majority of HIE stage III 75 (96.1%) were expired and this is comparable with the studies where HIE stage III had highest mortality rate.[17,18] Similarly, we compared outcome (discharged vs expired) with different stages of AKI but it was not found to be significant as p value was >0.05. In the study, we found 27 (79.4%) subjects of AKI stage I, 7 (100%) subjects of AKI stage II and 10 (90.9%) of AKI stage III died. Also, association between different stages of HIE and different stages AKI was found to be statistically insignificant in our study.

Limitations

Limitations of current study were, in our study we have used KDIGO classification for defining AKI which require an increase of serum creatinine by >0.3 mg/dl over the baseline values within a 48-hours period and a significant renal injury event during the first days of life may not necessarily increase the serum creatinine level to >0.3 mg/dl over the high baseline levels often seen immediately after birth. Also in our study, we couldn't be able to define AKI in subjects who died before completing 48 hours of life. Therefore, there is high chance of missing AKI in first 48 hours of life. Hence, we need a more sensitive definition of AKI and more reliable biomarkers. In our study, as we have not used urine output criteria of KDIGO classification to define Acute Kidney Injury, there is high chance of missing oliguric type of AKI which is common in advanced stages of AKI. This might be the reason behind having only few cases of AKI stage 3 in our study. Sample size of our study was small due to COVID-19 pandemic, therefore results cannot be applied on large population. Also this was a single center based observational study, so there is a need of multicentric study to be conducted on a large population.

CONCLUSION

From this study, it can be inferred that acute kidney injury is commonly associated with hypoxic ischemic encephalopathy but more frequently seen in advanced stage of HIE (III). There is high mortality rate associated with AKI in HIE. However, mortality is more common in advanced stage of HIE (III). Therefore, it is better to screen all the birth asphyxia cases for AKI so that they can be detected early and managed accordingly. In addition, a single normal value of blood urea/serum creatinine cannot exclude AKI, and serial monitoring is important.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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