Original Research Article

Study of incidence of acute kidney injury in asphyxiated neonates with hypoxic ischemic encephalopathy

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Received: 22 August 2020
Accepted: 08 October 2020

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ABSTRACT

Background: Perinatal asphyxia causes multi organ dysfunction resulting in renal (50%) and neurological (28%) compromise with 1.4% of hypoxic ischemic encephalopathy (HIE) and almost 20% death in India. Early recognition of acute kidney injury (AKI) is important in babies with HIE to facilitate appropriate fluid and electrolyte management for a stable biochemical milieu is vital.

Methods: A prospective case control study was done in Patna Medical College and Hospital, Patna between January 2019 and March 2020. 70 term asphyxiated neonates with HIE as cases and 70 healthy neonates as control were taken. AKI on basis of p RIFLE criteria and HIE on the basis of 5 minute APGAR score were determined and correlated.

Results: 58.6% cases of AKI with 73% pre renal and 61% non-oliguric type were found in asphyxiated neonates with HIE blood urea and serum creatinine values were significantly higher in asphyxiated babies than control group babies (p<0.0001).

Conclusions: The extent of AKI is directly proportional to severity of HIE.

Keywords: AKI, HIE, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia is a very common problem which significantly contributes to neonatal morbidity and mortality. The World Health Organization has characterized perinatal asphyxia as a lack of blood flow or gas exchange to and from the fetus in the period immediately before, during or after birth process. Globally this accounts for about 23% of all neonatal deaths. Perinatal Asphyxia ranks the second most important cause of neonatal death.¹ It is assessed with help of APGAR score.² An APGAR score of <7 at one minute of life is suggestive of perinatal asphyxia.³

The hypoxia and ischemia due to perinatal asphyxia causes multi organ dysfunction resulting in renal (50%) and neurological (28%) compromise, with 1.4% of HIE cases and almost 20% death in India.⁴¹⁰

Various studies have shown the significant differences in incidence of AKI between the asphyxiated neonates and normal babies.¹¹,¹² Further the incidence of AKI ranged from 0.4% of live births to 3.5% of hospital admission to 8% of admission to neonatal intensive care unit.¹³,¹⁴ There is a high incidence of AKI among the asphyxiated term infants (50-72%).¹⁵,¹⁶ The presence of perinatal asphyxia and its severity appear to correlate with increasing incidence of AKI.¹⁵,¹⁷ Asphyxia is an important cause of AKI and transient kidney impairment with adverse effects, especially in the first five days of birth.¹⁸,¹⁹ The kidney is the most damaged organ in asphyxiated full-term infants.¹⁹

As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxic ischemic episode, which if prolonged may even lead to irreversible cortical necrosis.¹³ Early recognition...
of AKI is important in babies with HIE to facilitate appropriate fluid and electrolyte management as a stable biochemical milieu is vital.

**Aims and objectives**

To determine the incidence and pattern of AKI in asphyxiated neonates with HIE; and to correlate the AKI with HIE staging.

**METHODS**

This was a prospective case control study done in Neonatal Intensive Care Unit and post natal ward of Patna Medical College and Hospital, Patna, Bihar, India during the period from January 2019 to March 2020

**Inclusion criteria**

For study group: 1) gestational age more than 37 completed weeks, 2) APGAR score less than 7 at 5 minutes after birth with HIE, 3) delayed cry more than 5 minutes with HIE, 4) need for positive pressure ventilation for more than 1 minute.

For control group: 1) gestational age more than 37 completed weeks, 2) no signs of birth asphyxia, 3) baby cried immediately after birth, 4) APGAR score more than 7 at 1 minute, 5) mothers with no history of any medications which could affect the neonatal health.

**Exclusion criteria**

For study group: 1) Major Congenital anomalies of the Kidney and Urinary tract, 2) Neonates with medical conditions that can affect renal functions, like – Septicaemia, Respiratory distress syndrome etc. 3) Mother taking any medications which could affect the neonatal renal function test, 4) Neonates less than 37 completed weeks, 5) Neonates on any nephrotoxic drugs.

**Method**

70 term asphyxiated neonates who fulfilled the inclusion criteria were enrolled in the study. Control group included 70 healthy babies.

Detailed examination of all the babies were done and findings of physical examination and systemic signs were recorded including their gestational age, birth weight and relevant perinatal and natal history.

On the basis of APGAR score at 5 minutes, asphyxiated neonates were further grouped into: mild- score of 6 or 7; moderate- score of 4 or 5; severe- score of 3 or less.

All neonates with clinical features of hypoxic ischemic encephalopathy (HIE) were staged by Sarnat and Sarnat scoring system. All the enrolled babies were subjected to ultrasonography of KUB within 24 hours of birth to rule out any congenital malformations of the urinary tract.

All these babies were managed as per standard protocols of the department.

Laboratory tests included random blood sugar, CBC, blood urea, creatinine, Na+ and K+, initially within the first 24 hours of life, and subsequently on 3rd or 4th day of life.

3 ml blood was drawn under aseptic precautions and was evaluated for blood urea (Berthelot method), serum creatinine (Jaffé’s test), and serum electrolytes (electrolyte analyser). AKI was classified according to p RIFLE criteria.31

The p RIFLE scale, for early detection and classification of the AKI severity is currently widely accepted, (p: pediatric, R: risk, I: injury, F: failure, L: loss, E: end stage).

**Risk:** 1.5 fold increases in S-creatinine or GFR decrease by 25% or urine output <0.5 ml/kg per hour for 6 hours.

**Injury:** Two fold increase in S-creatinine or GFR decrease by 50% or urine output <0.5ml/kg per hour for 12 hours.

**Failure:** Threefold increase in S-creatinine or GFR decrease by 75% or urine output <0.3 ml/kg per hour for 12 hours.

**Loss:** Complete loss of kidneys function for more than 4 weeks.

**ESRD:** Complete loss of kidneys function for more than 3 months.

GFR was calculated using formula: K × (height in cm) / serum creatinine K=0.45.

Oliguricrenal failure was diagnosed if urine output was less than 1 ml/kg/hour.

Neonates having abnormal renal functions 72-96 hours after birth, their laboratory parameters were monitored every day till recovery or death.

Other relevant tests like ABG, fractional excretion of Sodium, cardiac monitoring were done as per clinical situations.

Urine output was monitored by applying plastic collection bag or in a few cases by catheterization.

Asphyxiated neonates who after adequate management as per standard protocols had urine output persistently <1 ml/kg/hour were diagnosed to have intrinsic AKI. All
neonates with AKI underwent ultrasound imaging of the kidneys to detect changes in size, echotexture and cortico-medullary differentiation. Delayed cry after more than 5 minutes of birth. Need for positive pressure ventilation for more than 1 minute to resuscitate the baby. Mild, moderate or severe hypoxic ischemic encephalopathy as per Sarnat and Sarnat scoring system.

Thorough clinical and Neurological examination was done for all the neonates included in the both groups.

**Urinary samples:** Urine samples were collected using sterile urine collection bags within 24 hours of life and analysed immediately in the laboratory. Urinary uric acid was estimated by auto-analyser by enzymatic assay-Uricase method. Urinary creatinine was estimated in the same instrument by using modified kinetic Jaffé’s method.

**Statistical analysis**

SPSS software version 16.0: SPSS, Chicago, IL, USA.

**RESULTS**

Of the 70 asphyxiated neonates with HIE, 41 (58.6%) had AKI. while in control group no case of renal impairment was seen (Table 1).

**Table 1: Incidence of acute kidney injury in case and control group.**

| Acute kidney injury | Cases (%) | Controls (%) |
|---------------------|-----------|--------------|
| Present             | 58.60     | 00           |
| Absent              | 41.40     | 100          |
| Total               | 100       | 100          |

In our study AKI was predominantly prerenal type (73.2%). 26.8% cases were due to intrinsic renal damage. 60.97% cases had urine output >0.5 ml/kg/hr, while 39.03% were of oliguric type (Table2).

**Table 2: Distribution of type of AKI in cases.**

| Type of AKI | Structural | Functional |
|-------------|------------|------------|
| Prerenal    | (N=29)     | 70.73 %    |
| Intrinsic   | (N=12)     | 29.27 %    |
| Oliguric    | (N=16)     | 39.03 %    |
| Non oliguric| (N=25)     | 60.97 %    |
| Total       | 100 %      | 100 %      |

9.1% neonates of type I HIE had AKI in our study, insignificant number as only one case were found in pre renal, intrinsic, oliguric and non-oliguric variety.54.3% of neonates have type II HIE and 81.5% had incidence of AKI. Predominant type of AKI in type HIE babies was pre renal (83.9%) and non-oliguric type (64.5%).

**Table 3: Incidence of AKI in correlation with stages of HIE.**

| HIE staging | No. of neonates with AKI among HIE | Type of AKI |  |
|-------------|-----------------------------------|-------------|---|
| Prerenal    | Intrinsic                         | N=29        | N=12 |
| Stage I (N=22) (31.4%) | 02 (9.1%) | 01 (50%) | 01 (50%) |
| Stage II (N=38) (54.3%) | 31 (81.5%) | 26 (83.9%) | 05 (16.1%) |
| Stage III (N=10) (14.3%) | 08 (80%) | 02 (25%) | 06 (75%) |
| Total (N=70) | (100%) | N=41 | N=29 | N=12 |

Only 14.3% of neonates in this study had type III HIE with 80% renal involvement. 75% cases in this group had intrinsic renal disease with equal percentage (50%) having oliguric and non-oliguric variety (Table 3 and Table 4).

**Table 4: Incidence of AKI in correlation with stages of HIE.**

| HIE staging | No. of neonates with AKI among HIE | Type of AKI |  |
|-------------|-----------------------------------|-------------|---|
| Prerenal    | Intrinsic                         | N=16        | N=25 |
| Stage I (N=22) (31.4%) | 02 (9.1%) | 01 (50%) | 01 (50%) |
| Stage II (N=38) (54.3%) | 31 (81.5%) | 11 (35.5%) | 20 (64.5%) |
| Stage III (N=10) (14.3%) | 08 (80%) | 04 (50%) | 04 (50%) |
| Total (N=70) | (100%) | N=41 | N=16 | N=25 |

**Table 5: Distribution of cases and controls based on urine output.**

| Urine output | Total no. of cases (N=70) | Cases with AKI (N=41) | Control group (N=70) |
|--------------|----------------------------|-----------------------|----------------------|
| <0.5 ml/kg/hr| 16 (22.9%)                 | 16 (100%)             | 00 (0%)              |
| 0.5 ml/kg/hr | 54 (77.1%)                 | 25 (46.3%)            | 70 (100%)            |
| Total        | 70 (100%)                  | 41 (100%)             | 70 (100%)            |

In our study 22.9% neonates had urine output less than 0.5 ml/kg/hour and all of them had features of AKI, while 77.1% neonates had urine output more than 0.5 ml/kg/hr, of whom 46.3% had AKI. None of the neonates in control group had AKI (Table 5).

The mean blood urea (p value≤0.0001) and creatinine (p value≤0.0001) levels were significantly higher in study group neonates (Table 6).
Mean serum creatinine was 1.26 mg/dl in stage I HIE babies, 2.0 in stage II and 2.62 in stage III babies. The level of serum creatinine was statically significant (p<0.0001) in stage I and stage III babies.

**DISCUSSION**

Perinatal asphyxia results in damage of various vital organs if hypoxia is prolonged for more than 5 minutes either due to lack of oxygen or lack of proper perfusion. Kidney and brain are the most affected major organs. Kidneys are found to be very sensitive to oxygen deprivation and if subjected to prolonged deprivation, irreversible renal damage is very common.

In the present study biochemical parameters- serum creatinine, blood urea, serum sodium, serum potassium and urine output needed for diagnosis of renal dysfunction were assessed in both study group and control group and a significant difference in both group observed.

In this study 58.6% asphyxiated babies with HIE had AKI. In a similar study Gopal has found the incidence of AKI 64% which is further corroborated by various other studies. But contrary to our study Gupta et al and Agrawal et al had significantly higher incidence of AKI (72% and 75.5%) respectively.

In our study 73% cases had prerenal AKI and 27% intrinsic AKI. Non-oliguric AKI was observed in 61% case while oliguric AKI was observed in 39% cases. Various studies have similar findings. But contrary to our study Gupta et al had observation of 78.8% incidence of non-oliguric AKI, while Jayshree et al has reported 30.8% non-oliguric. In our study incidence of AKI in those asphyxiated babies who have suffered from HIE were studied and we observed that 9.1% neonates of type I HIE had AKI, of which 50% had pre renal and 50% intrinsic renal disease. Also in this group 50% cases had oliguric and 50% non-oliguric problem.

54.3% of neonates have type II HIE and 81.5% had incidence of AKI. Predominant type of AKI in type HIE babies was pre renal (83.9%) and non-oliguric type (64.5%).

Only 14.3% of neonates in this study had type III HIE with 80% renal involvement. 75% cases in this group had intrinsic renal disease with equal percentage (50%) having oliguric and non-oliguric variety.

Almost similar observations were made by Agrawal et al. Although in our study only 9% AKI cases were found in babies with grade I HIE, but in the study by Agrawal et al 53% cases of AKI were observed with 100% pre-renal type.

In this study blood urea and serum creatinine values were significantly higher in asphyxiated babies than control group babies (p<0.0001). The studies by Gopal and Agrawal et al have similar findings.

The level of serum creatinine was significantly higher in stage III HIE babies than stage II and I babies (p<0.0001). Medani et al has similar observation in his study.

**CONCLUSION**

Perinatal asphyxia is an important cause of HIE with neonatal AKI. Monitoring the levels of blood urea, serum creatinine and serum electrolytes helps in early diagnosis and helps in proper management. In asphyxiated neonates, correlation of biochemical parameters with the urine output is very useful to ensure that the kidneys are functioning optimally, although urine output does not necessarily mean that renal functions are intact. There is direct correlation between serum creatinine with HIE, i.e. extent of AKI is directly proportional to HIE and its staging.

**Funding: No funding sources**

**Conflict of interest: None declared**

**Ethical approval: The study was approved by the Institutional Ethics Committee**

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Cite this article as: Chaudhary R, Tiwari AK, Usmani F. Study of incidence of acute kidney injury in asphyxiated neonates with hypoxic ischemic encephalopathy. Int J Contemp Pediatr 2020;7:2205-9.