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Effect of perinatal asphyxia on renal function in term neonates- a prospective study

Dr. Jithin Chittethu Shaji*, Dr. Jayaram Sankar**

**Senior Resident, Dept. of Pediatrics, Govt. T.D. Medical college Alappuzha*

***Additional Professor, Dept. of Pediatrics, Govt. T.D. Medical college Alappuzha*

Section 1. Abstract:

Section 1.1. Background- Perinatal asphyxia, with an estimated incidence of 1-10 per thousand live births, is a major factor that can cause neonatal mortality and long term neurological morbidity. Kidney is the most affected organ by hypoxic damage. Many studies have reported high incidence of renal injury in babies with asphyxia. Early recognition of renal injury is vital in order to maintain fluid and electrolyte homeostasis.

Section 1.2. Objectives-

1. To assess the renal function in term neonates with perinatal asphyxia and to compare that with non-asphyxiated neonates.
2. To assess whether the degree of renal dysfunction among term newborns with perinatal asphyxia is related to the severity of hypoxic ischemic encephalopathy.

Section 1.3. Methods- This study was a prospective cohort study, done in the neonatal intensive care units of Govt. T.D. Medical College Hospital, Alappuzha during a period of one and half years. 25 neonates with perinatal asphyxia and 25 babies without perinatal asphyxia were selected according to the inclusion and exclusion criteria. Neurological staging of hypoxic ischemic encephalopathy was done. Blood and urine samples were collected at 24- 36 hours and 72-96 hours of life. Blood urea(BU), serum creatinine and urine β2 microglobulin values of two groups were compared.

Section 1.4. Results- There was a significant increase in blood urea, day 2 serum creatinine and urine β2 microglobulin values in asphyxiated newborns. Percentage of babies with abnormal urinary β2 microglobulin increased with the severity of hypoxic ischemic encephalopathy(HIE). 12% of asphyxiated babies developed acute renal injury on day 2, out of which 66.7% were intrinsic type.

Section 1.5. Interpretation and Conclusion - Alteration in renal function parameters is more frequent in newborns with perinatal asphyxia compared to non-asphyxiated babies. Abnormality in urinary β2 microglobulin is related to the severity of neurological damage. A small proportion of babies with asphyxia developed acute kidney injury, predominantly, intrinsic renal failure.

Section 2. Key words- Acute kidney injury; Hypoxic ischemic encephalopathy; Perinatal asphyxia; Urine β2 microglobulin.

Section 3. Introduction

Perinatal asphyxia remains a major problem in the neonatal intensive care units and is a significant cause of morbidity and death in both term and preterm neonates. The incidence of perinatal asphyxia is estimated to be between 1 and 10 per 1000 live births and is influenced by the birth weight and gestational age of the baby and also by the regional availability of medical resources [1]. Asphyxia leads to a redistribution of cardiac output to maintain cerebral, cardiac, and adrenal perfusion, seriously compromising renal, gastrointestinal, and skin perfusion [2-5].

Corresponding author: Dr. Jithin Chittethu Shaji, Chittethu

Hypoxia and ischemia can cause damage to almost every tissue and organ in the body [2]. Kidney is the most commonly injured organ. The incidence of renal injuries in asphyxiated babies have been reported between 50–72 percent in various studies [2,6-9]. As kidneys are very sensitive to hypoxia, renal insufficiency may occur within 24 hours of a hypoxic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis [10]. Asphyxia is the main cause of transient renal impairment or acute renal failure in neonates [11,12]. Early recognition of renal damage is therefore paramount in neonates with hypoxic ischemic encephalopathy (HIE) to facilitate appropriate fluid and electrolyte management. This study was conducted to compare the renal function in term asphyxiated neonates with non-asphyxiated newborns and to assess whether the degree of renal dysfunction among term babies with perinatal asphyxia is related to the severity of hypoxic ischemic encephalopathy. It was a prospective study carried over a period of one and half years.

Section 4. Materials and methods

Study design: Prospective cohort study.

Study setting: Newborn intensive care units in T.D Medical College, Alappuzha, Kerala.

Study period: One and half years (February 2015- July 2016)

Study population: Newborns admitted in Neonatal intensive care units.

Ethical considerations- Permission to conduct this study was obtained from Institutional Research Committee and Ethical Committee of Govt. T.D. Medical College, Alappuzha.

Section 4.1. Inclusion criteria

For Exposed cohort

Babies born at term (≥37 weeks) with perinatal asphyxia as evidenced by 3 or more of the following [7,13,14]

a. NST changes suggestive of fetal distress

b. APGAR score ≤6 at 5 min

c. Meconium stained liquor

d. Fetal bradycardia

e. Clinical evidence of HIE within 24 hours of birth

f. Positive pressure ventilation for ≥1 min after birth.

For Unexposed cohort

Babies born at term without perinatal asphyxia, matched for time and sex, not meeting the above criteria, but need investigations for some other problems, which will not interfere with renal function.

Section 4.2. Exclusion criteria

For both exposed and unexposed cohort

One or more of the following,

a. Babies with septicemia, Rh incompatibility

b. Major congenital malformations

c. Babies who received nephrotoxic drugs before blood sample collection

d. Babies whose mothers had eclampsia, septicemia, renal diseases and cyanotic congenital heart diseases or who had received nephrotoxic drugs

e. Antenatally detected genitourinary abnormality in fetus.

Section 4.3. Sample size

25 in exposed group and 25 in unexposed group

Based on earlier studies, the incidence of renal dysfunction in asphyxiated newborns (exposed group) was expected to be about 50%. Assuming an incidence of up to 10% renal dysfunction in non-asphyxiated newborns (unexposed group), a sample size of 25 per group was required to pick up the difference with 90% power and 95% confidence interval.

Formula applied for calculating sample size [15]

$$\frac{[(Z_{\alpha/2}+Z_{1-\beta})^2]x\{[P1x(1-P1)] + [P2 x (1-P2)]\}}{(P1-P2)^2}$$

Giving P1 as 50% and P2 as 10%, a sample size of 25 was obtained.

Section 4.4. Study method

Exposed (cases) and unexposed groups (controls) were taken as per the inclusion criteria and exclusion criteria. Newborn resuscitation was done according to the guidelines recommended by the American Academy of Pediatrics in 2010. After birth, babies were examined for weight, gestational age (by Modified New Ballard scoring system) and major congenital anomalies. All babies were uniformly managed as per standard neonatal intensive care unit guidelines. Neurological staging of hypoxic ischemic encephalopathy was done using Sarnat and Sarnat scoring system between 24-48 hours after birth [16]. Urine and blood samples were collected for appropriate investigations. Acute Kidney Injury in this study was defined as a serum creatinine >1.5 mg/dl [17]. FeNa (fractional excretion of sodium) >2.5% was considered as an indicator of intrinsic renal failure [18]. Throughout the study, a strict fluid and electrolyte balance was ensured for asphyxiated newborns from day one of birth. Babies were closely followed up till discharge or the first week of birth.

Section 4.5. Procedure of collection of samples

Two milliliters of venous blood in plain plastic tubes and urine samples (supra-pubic aspiration or voided specimen) were collected at 24-36 hours (postnatal day 2, hereafter mentioned as day 2) and 72-96 hours of life (postnatal day 4, hereafter mentioned as day 4). Blood urea (Urease method), serum creatinine (Jaffe's method), urine sodium (Ion selective electrode method) & urine creatinine (Jaffe's method) were tested using computerized auto analyzer. Urine β2 microglobulin was tested using enzyme linked immunosorbent assay kit. Considering the cost and feasibility, urine β2 microglobulin was tested only once from the first urine sample collected at 24-36 hours of life. Fractional excretion of sodium was calculated as [10,18]

- Fractional excretion of sodium (FeNa)= Urine sodium X Plasma creatinine X 100/ {Plasma sodium X Urine creatinine}

Section 4.6. Statistical analysis-

Data were analyzed using computer software, SPSS 17. The quantitative variables have been summarized as mean with standard deviation. The statistical significance of association between cases and controls was tested using Karl Pearson's Chi squared test. For all statistical evaluations, a probability value, P <0.05 was considered significant.

Section 5.1. Results

25 exposed and 25 unexposed babies were taken from the total 3478 deliveries that took place during this time period, who met the inclusion criteria. Both study groups were comparable with respect to gestational age, sex, birth weight, mode of delivery and in maternal serum creatinine values (**Table 1)**. A significant increase in blood urea, serum creatinine and urinary β2 microglobulin was noticed in asphyxiated neonates (**Table 2**). As the severity of hypoxic ischemic encephalopathy increased, higher percentage of babies had abnormal urine β2 microglobulin (**Table 3**). 12 % of asphyxiated newborns developed acute kidney injury (**Table 2**), 66.7% were intrinsic in nature (**Table 4**).

Table 1: Clinical characteristics of the study groups

Characteristics	Exposed cohort N=25	Unexposed cohort N=25
Gestational age (weeks)	38.3 ± 1.1	38.5 ± 1.1
Male gender (n, %)	14 (56%)	14 (56%)
Birth weight (kg)	2.9 ± 0.4	3 ± 0.4
Caesarian delivery (n, %)	14 (56%)	13 (52%)
Maternal serum creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2

Table 2: Comparison of selected variables in study groups

Variables	Exposed cohort N=25	Unexposed cohort N=25
Abnormal urine β2 microglobulin (n, %)	11 (44%)	4 (16%)
Mean urinary β2 microglobulin	1461.5 ± 467.2	90.3 ± 19.8 (P=0.03) *
Mean blood urea day 2 (mg/dl)	30.4 ± 12.8	25.5 ± 9.1 (P=0.04) *
Mean blood urea day 4 (mg/dl)	31.2 ± 18.7	20.3 ± 8 (P=0.02) *
Mean serum creatinine day 2 (mg/dl)	1.1 ± 0.4	0.7 ± 0.3 (P=0.009) **
Mean serum creatinine day 4 (mg/dl)	0.7 ± 0.3	0.5 ± 0.2 (P=0.422) **
Acute kidney injury on day 2 (n, %)	3 (12%)	0 (0)
Acute kidney injury on day 4 (n, %)	1 (4%)	0 (0)

*significant at 0.05 level

**significant at 0.01 level

Table 3: Comparison of urinary β2 microglobulin based on HIE stage in case group

Variable		HIE 1	HIE 2	HIE 3	χ^2	P
Urine β2 microglobulin	Normal	13 (76.5%)	1 (16.7%)	0 (0)	9.2*	0.010
	Abnormal	4 (23.5%)	5 (83.3%)	2 (100%)		

*significant at 0.05 level.

HIE- hypoxic ischemic encephalopathy

Table 4: Fractional excretion of sodium of those who developed AKI

Fractional excretion of sodium (FeNa)	Serum creatinine day 2 >1.5 mg/dl	Percentage
<1%	1	33.3%
>2.5%	2	66.7%

AKI- acute kidney injury

Section 5.2. Discussion:

This study found out that the blood urea and day 2 creatinine values were significantly elevated in asphyxiated neonates (**Table 2**). A study by B.D. Gupta et al. [10] and Vandana et al. [19] reported that the values of mean blood urea and mean serum creatinine were significantly higher in asphyxiated babies compared to non-asphyxiated neonates (P<0.001). On day 4, mean creatinine values of asphyxiated babies almost matched the normal babies, indicating that the creatinine values of hypoxic babies returned to normal as postnatal age advanced. (**Table 2**). Only a few studies like Roberts et al. [20] mentioned about such an observation. Urine β2 microglobulin was abnormal in 44% of asphyxiated babies and 16 % of non-asphyxiated newborns (**Table 2**). This shows that, asphyxiated newborns had a significant elevation in urinary β2 microglobulin, when compared to non- asphyxiated neonates (**Table 2**). Studies of Aggarwal et al. [17], Askenazi et al. [21] and Banerjee et al. [22] showed similar findings.

Urinary β2 microglobulin was abnormal in 23.5%, 83.3% and 100% of HIE 1, HIE 2, HIE 3 babies respectively, which means, as the severity

of neurological damage increased, more asphyxiated babies had urinary β2 microglobulin in the abnormal range (**Table 3**). This might highlight the significance of using this urinary marker as an early sign of renal injury.

As per our definitions on acute kidney injury (AKI) [17] (serum creatinine >1.5mg/dl), only 3 cases had AKI on day 2 of life (**Table 2**). Hence in this study, AKI developed in only 12% of asphyxiated neonates, while none of the non-asphyxiated babies developed acute kidney injury. However, in most other studies [7,10], the incidence of AKI is much higher in asphyxiated newborns. This shows that, the incidence of AKI varies with various interpretation of definition and also upon the criteria chosen for selecting asphyxiated babies. On day 2, 66.7% of cases with serum creatinine >1.5 mg/dl had intrinsic renal failure, only 33.3% had pre-renal failure (**Table 4**). This is in contrast with other studies [23,24], where the incidence of pre-renal failure was more compared to intrinsic renal failure. However, in order to strictly find out which type of renal failure actually predominates in asphyxia, more number of AKI cases should be there, which is actually a limitation of my study. Another limitation is that, umbilical cord pH and base deficit were not accounted for defining case groups. Only one case continued to have renal failure on day 4, that indicates nearly two-thirds of babies recovered from AKI by day 4, which showed the importance of strict electrolyte and fluid balance that had employed in this study.

Section 6. Conclusion:

A significant elevation of renal function parameters was noted in asphyxiated neonates. Increased severity of asphyxia resulted in incremental percentage of babies with abnormal urinary β2 microglobulin. A small proportion of asphyxiated neonates developed acute kidney injury, majority of them had intrinsic renal failure. Two-thirds of the babies recovered from AKI by day 4, signifying the importance of ensuring adequate fluid and electrolyte balance.

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