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ROLE OF URINARY URIC ACID AND CREATININE RATIO IN DIAGNOSIS OF PERINATAL ASPHYXIA

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ABSTRACT **Background:** Perinatal asphyxia is a common neonatal condition and contributes significantly to neonatal morbidity and mortality. There is a need to identify neonates with asphyxia who will be at risk for hypoxic ischemic encephalopathy (HIE) and multi-organ dysfunction. **Objectives:** To evaluate prospectively the value of measuring urinary UA/ Cr ratio in early spot urine samples in diagnosing perinatal asphyxia and to assess the relationship between the urinary UA/Cr ratio and the severity of HIE. **Methods:** The study was conducted in babies born at K V G medical college and Hospital, Sullia from October 2018 to May 2020. The urine sample from 55 asphyxiated neonates comprising cases and 55 comprising controls constituted the material for the study. **Results:** Urinary uric acid/creatinine ratios were found to be higher in asphyxiated infants (2.58 ± 0.94) when compared to those in control group (0.87 ± 0.17). The cut-off UUA/Cr value of 1.03 has 92.72% sensitivity with a specificity of 76.36% and has a positive predictive value of 79.68% with a negative predictive value of 91.30%. **Conclusion:** UUA/Cr concentration increase after birth asphyxia and is non-invasive, sensitive and cost-effective method for assessment of asphyxia and its outcome.

KEYWORDS : perinatal asphyxia, urinary uric acid/ creatinine ratio, hypoxic ischemic encephalopathy (HIE).

INTRODUCTION

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Globally, it is estimated to account for 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year [1]. Data from National Neonatal Perinatal database suggests that perinatal asphyxia contributes to almost 20% of neonatal deaths in India [2]. An estimated 1 million children who survive birth asphyxia live with chronic neurodevelopmental morbidities, including cerebral palsy, mental retardation, and learning disabilities[1]. Although asphyxia is associated with multiple organ injuries, management still focuses on supportive care. Hence there is a need to identify infants who will be at high risk for HIE and early neonatal death as a consequence of perinatal hypoxia.

In a term infant with perinatal asphyxia renal, neurologic, cardiac and lung dysfunction occurs in 50%, 28%, 25% and 23% cases respectively. The extent of multi-organ dysfunction determines the outcome of an asphyxiated neonate with either the neonate succumbing as a consequence of organ damage or recovering completely. HIE refers to the central nervous system dysfunction associated with perinatal asphyxia and has the potential to cause serious long term neuromotor sequelae [3].

Brief hypoxia impairs cerebral oxidative metabolism leading to an anaerobic glycolysis to generate ATP. Lack of ATP and increase excitotoxin will leads to cellular damage and accumulation of ADP and AMP, which is later catabolized to adenosine, inosine and hypoxanthine. Uninterrupted tissue hypoxia and reperfusion injury causes oxidation of hypoxanthine to xanthine and uric acid leading to an increase in uric acid in blood and urine.[4]

Despite the increasing understanding of the mechanisms leading to and resulting from neonatal asphyxia, early diagnosis of brain damage following hypoxic-ischemic events still remains the hardest difficulties in neonatal care. Several studies have been conducted to evaluate better markers that help identify asphyxia, including electronic fetal heart monitoring, low Apgar scores, cord pH, electroence phalograms, computed tomography and magnetic resonance imaging scans and Doppler flow studies.[5]

Analysis of xanthine, hypoxanthine, neuron-specific enolase, brain-specific creatine kinase and inflammatory cytokines (TNF-α, IL-1b, IL-8, IL-6) are time consuming, costly and not routinely available. Previous studies have demonstrated higher cord blood hypoxanthine level concentrations in hypoxic fetuses. Additional studies have indicated higher uric acid concentration in mothers with pre-eclampsia. This study was conducted to evaluate the utility of urinary UA/Cr ratio as noninvasive, easy, cheap, and early biochemical means of asphyxia diagnosis.[6]

METHODOLOGY

This prospective study was conducted in Neonatal division of department of Paediatrics, KVG medical college, Sullia, for a period of 18 months from December 2018 to May 2020. A Case study of 55 cases (Neonatal Asphyxia) and 55 Controls (healthy newborns) were undertaken in assessing the urinary UA/Cr ratio as a marker of neonatal asphyxia.

Inclusion criteria:

Case group- Neonates with gestational age of >/= 36 weeks, appropriate for gestational age and those with asphyxia (at least 3 of the following - non-reassuring Non-stress test on continuous electronic fetal monitoring and/or by thick meconium stained amniotic fluid, APGAR score of <7 at 1 minute of life, resuscitation with >1 minute of positive pressure ventilation before spontaneous breathing, metabolic acidosis in umbilical artery blood, HIE.

Control group - healthy neonates, appropriate for gestational age, without signs of perinatal asphyxia - normal fetal heart rate, clear liquor and one minute APGAR of >7.

Exclusion criteria:

Neonates with congenital malformations, maternal drug addiction, born to mothers consuming alcohol, who are smokers or who are on antiepileptics. Detailed maternal history, continuous electronic fetal monitoring, meconium staining of amniotic fluid, birth events, Apgar score and other

systemic effects of asphyxia were recorded. Gestational age was assessed by New Ballard scoring system. HIE was graded using Sarnat and Sarnat staging. Urine samples were collected within 6-24 hours of life and sent for the spot urine tests. Urinary uric acid was estimated by *Mispa Nano Auto Analyser* by spectrophotometric uricase method and Urinary creatinine by modified kinetic Jaffe's method.

The collected data was entered in Microsoft officeexcel and analyzed using SPSS statistics v20. Descriptive statistics like frequencies and percentages are used. Chi square test and t-test are used to describe the associations and correlations. The p value of < 0.05 was considered significant.

RESULTS

There were 35 females and 20 males in both groups. Incidence of Non Reassuring NST, thick MSAF, APGAR score <7 and hypotonia were significantly more in case group against control group. Urinary UA /Cr ratio is significantly higher in case group compared to control group. Out of 55 asphyxiated neonates, 19(34.54%) neonates had stage 1 HIE, 13(23.63%) neonates had stage 2 HIE, 7 (12.72%) neonates had stage 3 HIE. Details of baseline characteristics and various parameters have been tabulated in table 1. UUA/Cr ratios were significantly higher in infants with severe HIE (stage 3) (4.04 ± 0.43) when compared with infants with moderate HIE (stage 2) (3.15 ± 0.42) and those with mild HIE (Stage 1) (2.42 ± 0.58). The cut-off UUA/Cr value of 1.03 has 92.72% sensitivity with a specificity of 76.36% and has a positive predictive value of 79.68% with a negative predictive value (Figure 1).

Table 1: Comparison Of Baseline Characteristics And Various Parameters Between Asphyxiated Newborns And Control Group.

Characteristics		CASES	CONTROLS	P VALUE
Gender	Males	35 (63.63%)	35 (63.63%)	1.000
	Females	20 (36.36%)	20 (36.36%)	
Gestational Age	Preterm	2 (3.63%)	2 (3.63%)	1.000
	Term	35 (63.63%)	35 (63.63%)	
	Post term	18 (32.72%)	18 (32.72%)	
Mean Birth weight		3.08 ± 0.35	3.03 ± 0.37	0.4682
Non Stress Test	Reactive	9 (16.36%)	55 (100%)	<0.0001*
	Non Reactive	46 (83.63%)	0 (0%)	
Meconium Stained amniotic fluid	Present	19 (34.54%)	0 (0%)	<0.0001*
	Absent	36 (65.45%)	55 (100%)	
APGAR at 1 minute	7 to 10	0 (0%)	55 (100 %)	<0.0001*
	0 to 6	55 (100%)	0 (0%)	
APGAR at 5 minute	7 to 10	36 (65.45%)	55 (100 %)	<0.0001*
	0 to 6	19 (52.77%)	0 (0%)	
APGAR at 10 minute	7 to 10	43 (78.18%)	55 (100 %)	<0.0001*
	0 to 6	12 (21.81%)	0 (0%)	
Hypotonia	Present	20 (36.36%)	0 (0%)	<0.0001*
Seizures	Present	18 (32.72%)	0 (0%)	<0.0001*
Mean Urinary Uric Acid To Creatinine Ratio		2.58 ± 0.94	0.87 ± 0.17	<0.0001*
HIE	No HIE	16 (29.09%)	0 (0%)	<0.0001*
	Stage 1	19 (34.54%)	0 (0%)	
	Stage 2	13 (23.63%)	0 (0%)	
	Stage 3	7 (12.72%)	0 (0%)	

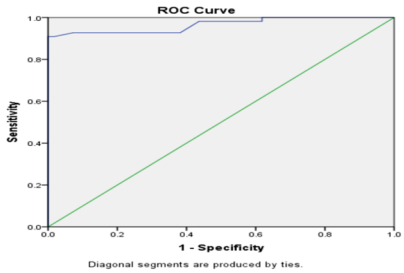

Fig 1: Roc Curve Analysis Of Uua/cr Ratio In Prediction Of Neonatal Asphyxia

DISCUSSION

Perinatal asphyxia is a devastating clinical condition because of its potential for causing permanent neurological damage, neonatal morbidity and mortality. The value of present biochemical markers for diagnosing asphyxia is inadequate and controversial.

The Apgar score has a limited role in predicting the immediate outcome, such as that of HIE and the long-term sequelae. The present study revealed significant increase in UUA/Cr ratio in early spot urine samples from asphyxiated newborns and higher levels of urinary UUA/Cr ratio in severe HIE. Similar results were published by Reem et al[6] who reported Urinary UUA/Cr ratio was higher in asphyxiated neonates (2.9 ±0.73) when compared with the controls (0.72±0.35) P<0.0001 and were significantly higher in infants with severe HIE (3.18± 0.61; p<0.001). (Table 2)

Pallab Basu et al[7] found that urinary UA/Cr Ratio was significantly higher in cases than control which is similar to our study (Table 3). There was significant difference between mean urinary UA/Cr ratio for Apgar score 4-6 compared to Apgar score 0 -3 (p 0.001) which is also similar to our study. Bader et al[8] found UUA/Cr ratio was higher in the asphyxiated group when compared to control group which is similar to our study (Table 3).

They found the positive predictive value of UA/Cr >1.2 was 78% and the negative predictive value was 72%, sensitivity was 74% and specificity 76% which was comparable to our study.

Table 2: Comparative Study Of Baseline Characteristics And Various Parameters Between Our Study And Other Studies.

Characteristics		Barder et al		Reem et al		Pallab basu et aal		Present study	
		Cases (n=18)	Controls (n=50)	Cases (n=40)	Controls (n=20)	Cases (n=31)	Controls (n=31)	Cases (n=55)	Controls (n=55)
Sex	Male	-	-	40%	70%	48%	61%	63.63%	63.63%
	Female	-	-	60%	30%	52%	39%	36.36%	36.36%
Mode of Delivery	Normal	28	90%	60%	70%	39%	84%	56.36%	70%
	Instrumental	31%	-	10%	10%	-	-	12.72%	3.63%
	Caesarean	39%	10%	30%	20%	61%	16%	30.90%	24.45%
Birth weight		3.211 ±0.450	3.60 ±0.300	3.25 ±0.543	3.32 ±0.442	2.42± 0.44	2.56 ±0.52	3.08 ± 0.35	3.03 ± 0.37

APGAR 1MIN 5MIN 10MIN	Min 2.43 Max 5.24-	Min 9.50 Max 9.77-	1(0-1) 3(1-5) -	9(8- 10) 9(8- 10) -	Min 2.43 Max 5.24-	Min 9.50 Max 9.77-	3.18 1.68 8 ± 0.96 8.93 ± 0.25	>7 >8 >9
Urinary uric acid to creatinine ratio	2.06±1.12	0.64 ±0.48	2.9±0.73	0.72± 0.35	3.1± 1.3	0.96 ±0.54	2.58±0.94	0.87 ±0.17

We found the UUA/Cr ratio to be a good, simple screening test for early assessment of perinatal asphyxia. Furthermore, there is a correlation between the UA/Cr ratio and the severity of the encephalopathy indicating the degree of injury at an early stage when other quantitative methods frequently cannot be carried out. However, this does not provide further prognostic information that must be obtained by other methods.

CONCLUSION

Urinary uric acid to creatinine ratio estimation from spot urine sample can be used as an non- invasive and early biochemical marker of birth asphyxia which biochemically supports the clinical diagnosis and severity grading of asphyxia by Apgar score. The cut-off UUA/Cr value of 1.03 has 92.72% sensitivity, 76.36% specificity, 79.68% positive predictive value and 91.30% negative predictive value.

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