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The Role of Urinary Uric Acid to Creatinine Ratio as a Marker of Perinatal Asphyxia and Its Severity in Newborns

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Abstract: *Perinatal asphyxia is one of the most important causes of neonatal morbidity and mortality in our country. Easily available biochemical markers are still not used routinely in diagnosis of perinatal asphyxia. Our study aims to use urinary uric acid to creatinine ratio to diagnose perinatal asphyxia and its severity. This prospective study was conducted at Dr. BSA Hospital, Delhi from March, 2015 to March, 2016. A total of fifty (50) asphyxiated and fifty (50) non-asphyxiated term newborns were included in the study. It was found that the urinary uric acid to creatinine ratio (UUA/Cr) is significantly ($p<0.001$) increased in asphyxiated newborns and its level is directly related to the severity of perinatal asphyxia. The above study shows that the spot urinary uric acid to creatinine ratio may be used as a biochemical marker for diagnosing and predicting the outcome of perinatal asphyxia.*

Key words: *Perinatal asphyxia, urinary uric acid/creatinine ratio*

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I. Introduction

Perinatal asphyxia contributes significantly to neonatal morbidity and mortality. Factors like poverty, ignorance and lack of medical facilities and obstetric care (only a third of deliveries being institutional) contribute significantly to the magnitude of the problem of perinatal asphyxia in our country Although a common condition, there is generally no accepted definition for birth asphyxia. It is a devastating clinical condition because of its potential for causing permanent damage, even death of the fetus or newborn baby. The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia.

At present the value of biochemical markers for diagnosing asphyxia is inadequate and controversial(1). Prediction of final outcome of perinatal asphyxia is important but formidable(2).The APGAR score has a limited role in predicting the immediate outcome such as that of HIE and the long-term sequelae(3). Several studies have shown that monitoring of cerebral function using non invasive techniques such as EEG within six hours of birth, cranial ultrasonography, cranial topography, doppler measurements of cerebral blood flow, somato-sensory evoked potentials, magnetic resonance imaging and estimation of neurophysiological markers such as CK-BB, brain specific LDH isomer, glutamate and neurone specific enolase in the cerebrospinal fluid are all useful in predicting both the immediate dysfunction and the long term outcome(2,4,5). But none of these facilities are routinely available except in a few tertiary care hospitals and/or in some of the teaching hospitals of our country. Several studies have been conducted to evaluate better markers that are easily available and help to differentiate asphyxial and non-asphyxial etiology in neonates.

Cellular metabolism requires adequate oxygen supply. Brief hypoxia impairs cerebral oxidative metabolism leading to an anaerobic glycolysis to generate ATP. During prolonged hypoxia, cardiac output falls, cerebral blood flow (CBF) is compromised and a combined hypoxic-ischemic insult produces further failure of oxidative phosphorylation and ATP production sufficient to cause cellular damage. Lack of ATP and increased excitotoxic cellular damage leads to an accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP) which is then catabolized to adenosine, inosine and hypoxanthine(6–10).

If there is uninterrupted tissue hypoxia and also reperfusion injury, hypoxanthine is oxidized to xanthine and uric acid in presence of xanthine oxidase leading to an increase in uric acid production, which comes out in blood from tissues and is excreted in urine.(6–10)

In the present study, an attempt has been made to ascertain whether urinary uric acid and creatinine ratio (UUA/Cr) can distinguish an asphyxiated from a non-asphyxiated term neonate and assess severity of asphyxia. These tests are routinely available in most centres, hence a comparative study was done to establish the usefulness as reported in some previous studies. An attempt was also made to find out whether APGAR score is still an important tool for diagnosis of birth asphyxia and its severity.

II. Methods

This prospective case control study was conducted on asphyxiated and non-asphyxiated term neonates recruited from Neonatal Intensive Care Unit (NICU) and Post natal wards of Dr. Baba Saheb Ambedkar Hospital, New Delhi from March 2015 to March 2016 after informed consent.

The study was approved by the scientific and ethical committees of the hospital

The cases and controls comprised of fifty asphyxiated and fifty non-asphyxiated neonates, respectively. The urinary samples from fifty cases and fifty controls were the material for the study. The case group included fifty neonates fulfilling the following criteria:

Inclusion criteria:

1. Gestational age ≥ 37 weeks, Appropriate for gestational age delivered vaginally or through lower segment caesarean section.
2. The neonates will be identified to have experienced perinatal asphyxia when at least 3 of the following are present.

A. APGAR score of <7 at one minute of life.
B. Resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration.
C. Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by sarnat and sarnat 1976.
D. Intrapartum signs of fetal distress, as indicated by non reassuring NST on continuous electronic fetal monitoring and /or by thick meconium staining of the amniotic fluid (TMSAF).
E. Profound metabolic or mixed academia (pH<7) in an umbilical artery blood sample, if obtained within 30 minutes of birth.

Exclusion criteria:

1) Congenital malformations.
2) Maternal drug addiction.
3) Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opiods (pharmacological depression).
4) Hemolytic disease of the newborn.
5) Neonates born to mothers consuming alcohol.
6) Neonates born to mothers who are smokers.
7) Neonates born to mothers on anti epileptics.

The control group included fifty term apparently healthy neonates appropriate for gestational age without signs of perinatal asphyxia as evidenced by normal fetal heart rate patterns, clear liquor and one minute APGAR score ≥7. All deliveries were attended by residents trained in neonatal resuscitation.

Detailed maternal history including antenatal and intrapartum events, APGAR score, sex and weight of the baby were recorded on the precoded Performa. Gestational age was assessed by New Ballard scoring system and a thorough clinical and neurological examination was done for all the neonates. Asphyxiated neonates were monitored for seizures, hypotonia, HIE and other systemic effects in the immediate neonatal period. Other causes of hypotonia, seizures, lethargy, poor feeding were ruled out with clinical assessment and relevant available investigations. The peripheral smear for erythrocyte morphology and reticulocyte count was used to document hemolytic disease of the newborn. HIE severity was graded using SARNAT and SARNAT staging(11).

Spot urine samples within 6-24 hours of birth were collected in sterilized disposable urine bag, were frozen at - 20°C and analysed. Urinary uric acid was estimated by spectrophotometric uricase method and urinary creatinine was estimated by using Jaffe's alkaline picrate method by auto analyzer ((Roch / Hitachi 917).

Statistical Analysis- Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. . Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. SSPS version 15, SAS9.2 was used for analysis of data. Microsoft Word and Excel have been used to generate graphs, tables etc.

III. Result

Samples and controls were gender matched(p=0.315).Gestational age , birth weight distribution and proportion of primigravida and multigravida mothers was statistically similar(p=0.277 , p=0.13 and p=0.057 respectively).Incidence of caesarean section and instrumental delivery was significantly more in case group(88%) as compared to control group(34%) with p<0.001. Reassuring NST and incidence of thick MSL is significantly more in case group against control group (P=0.004 and p<0.005).Incidence of low APGAR at 1minute,5minutes and 10 minutes was significant in cases as compared to control(p<0.001),thereby being important tool for diagnosis of birth asphyxia and its severity. The mean UUA/Cr ratio was found significantly higher in study group(2.58±1.09) as compared to control group(0.86±0.17)(P<0.001**) and also correlated significantly with HIE severity .

A significant correlation was also seen between the APGAR scores at 5 minutes and 10 minutes with HIE severity (p<0.001), although this correlation was not significant at 1 minute.

Table no. 1: Demographic Profile of Patients and APGAR scores

PARAMETER	ASPHYXIATED (n=50)	CONTROLS(n=50)
GENDER		
MALE	30	25
FEMALE	20	25
GEATATIONAL AGE		
TERM	32	50
POST DATED	13	0
POST TERM	5	0
BIRTH WT(Mean ± SD)	2.92 ± 0.36	3.02 ± 0.38
MATERNAL HISTORY		
PRIMI	28	26
MULTI	22	24
MODE OF DELIVERY		
NORMAL	28	49
INSTRUMENTAL	5	0
LSCS	17	1
NST		
REACTIVE	7	50
NON REACTIVE	43	0
TMSAF		
NEGATIVE	27	50
POSITIVE	23	0
APGAR SCORE AT 1 MIN		
< 7.0	50	0
>7.0	0	50
APGAR SCORE AT 5 MIN		
<7.0	18	0
>7.0	32	50
APGAR SCORE AT 10 MIN		
<7.0	9	0
>7.0	41	50

Table no.2 APGAR score further subdivided in neonates studied

APGAR score	Cases (n=50)		Control (n=50)	
	No	%	No	%
APGAR score at 1 min				
0-3	45	90.0	0	0.0
4-6	5	10.0	0	0.0
≥7.0	0	0.0	50	100.0
APGAR score at 10 min				
0-3	0	0.0	0	0.0
4-6	9	18.0	0	0.0
≥7.0	41	82.0	50	100.0

Table no.3 Comparison of Uua/Cr Ratio of cases and controls

UUA/Cr	Cases`	Controls
Min-Max	0.78-4.94	0.42-1.14
Mean ± SD	2.58±1.09	0.86±0.17

Table no.4 Correlation of urinary uric acid and creatinine ratio(UUA/Cr) withHIE status in cases studied

UAA/Cr	Total number of patients (n=50)	HIE stage				
		Not in HIE (n=14)	Stage I (n=16)	Stage II (n=14)	Stage III (n=6)	P value
Min-Max	0.78-4.94	0.78-2.65	1.62-3.48	2.18-3.92	3.72-4.94	<0.001**
Mean ± SD	2.58±1.09	1.35±0.57	2.70±0.66	2.90±0.56	4.37±0.43	

Table no.5 Sensitivity, Specificity and Predictive Values of UAA/Cr in prediction of Neo-natal asphyxia

UAA/Cr	Sensitivity	Specificity	PPV	NPV	Accuracy	Area Under ROC	P value
>1.14	84.00	94.00	93.33	85.45	89.00	0.963	<0.001**

The cut-off UAA/Cr value of >1.14 has 84% sensitivity with a specificity of 94% and has a positive predictive value of 93.33% with a negative predictive value of 85.45% with an accuracy of 89%.

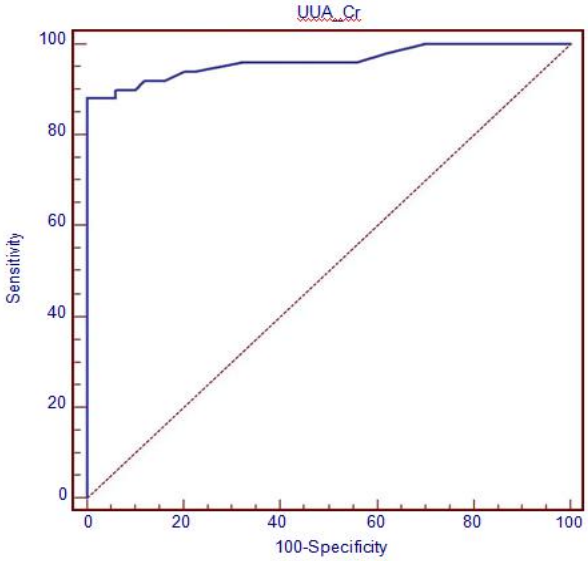

Figure 01: ROC analysis of UAA/Cr to prediction of Neo-natal asphyxia

IV. Discussion

Low APGAR score is commonly used as an indicator of asphyxia in neonates, but it may often be not available and may be low in premature infants (12). Other investigations may be required to support the diagnosis of asphyxia for early intervention. Blood pH values get quickly normalized after the onset of respiration, due to the elimination of carbon dioxide and cannot be relied upon specially in patients who are transferred from other centres. Additionally, lactate and base deficit are closely interconnected.

The present study revealed a significant increase in UA/Cr ratio in early spot urine samples from asphyxiated full term newborns and the study proved positive correlation between the urinary UA/Cr ratio and the severity (grading) of HIE (P< 0.001). Our results are similar to studies conducted by Pallab Basu et al(13), Bader et al(14), Akisu et al(15), Mehes et al(16) and Vandana Verma et al (17).

In the present study the cut-off UAA/Cr value of >1.14 has 84% sensitivity with a specificity of 94% and a positive predictive value of 93.33% with a negative predictive value of 85.45%, with an accuracy of 89% for neonatal asphyxia. Similar results were shown by Bader et al (14)and Chen et al(18) i.e. that the positive predictive value of Ua/Cr >1.2 was 78% and the negative predictive value was 72%.The sensitivity was 74% and specificity 76%.

Banupriya et al(19) stated that a cut off value of 2.34 Uric Acid / mg of creatinine can predict fatal

outcome in perinatal asphyxia. In our study, two hypoxic newborns who had UA / Cr ratio of 4.68, and 4.94 died although the number is small to make any definitive conclusion.

APGAR score was found to be significantly lower in asphyxiated newborns as compared to controls. Also a significant correlation was found between lower APGAR score at 5 and 10 minutes with HIE severity in our study. Similar results were found in the studies conducted by Salustiano et al(20), Ehrenstein et al(21). But value of APGAR score of < 7 at five minutes is still considered controversial by different studies and many neonatologist across the world(22,23).

V. Conclusion

Urinary UA/Cr ratio increases considerably after birth asphyxia, and the increase is associated with severity of HIE with a poorer outcome. Hence, UUA/Cr ratio might have an important role in diagnosing and predicting the outcome of perinatal asphyxia although there is a need for a large population based prospective study including preterm and term newborns to determine cut off values of urinary UA/Cr ratio for the severity of perinatal asphyxia.

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