Original research article

Utility of urinary uric acid and creatinine ratio as a marker of neonatal asphyxia: a comparative assessment

Sujit Kumar Baranala[1], Nitish Kumar[2]

[1]Senior Resident, Department of Pediatrics, Kalawati Saran Children Hospital, New Delhi, India.

[2]Senior Resident,Department of pediatrics, AIIMS, New Delhi,India.

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Abstract

Aim: to assess the utility of urine uric acid creatinine ratio (UA/Cr) as an additional marker of neonatal depression and birth asphyxia and it's utility as a potential prognostic indicator for the immediate outcome. **Material and methods:** This prospective observational study was carried out in the Department of Pediatrics, Kalawati Saran Children Hospital, New Delhi, India for 1 year in this study that included 200 newborns born. Newborns with encephalopathy were considered to have an unfavourable outcome. The urine UA/Cr was estimated in both groups.
Results: The mean differences of urine UA/Cr were statistically significant in birth asphyxia (3.26±1.37), and controls (2.02± 0.71). **Conclusion:** The urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia.

Keywords: UA/Cr, Biomarker, Birth asphyxia

Introduction

Perinatal asphyxia is a common neonatal problem and there is significant contribution to neonatal morbidity and mortality. In worldwide, birth asphyxia accounts for 26% of the 3.2 million stillbirths and 23% of the 4 million neonatal deaths each year.[1] Developing countries are more affected due to the lack of resources.

In India, due to birth asphyxia, between 250,000 to 350,000 infants die each year, mostly within the first three days of life. Perinatal asphyxia contributes to almost 20% of neonatal deaths in India as per the data by National Neonatal Perinatal database (NNPD). The contribution of ante-partum and intra-partum asphyxia are about 300,000 to 400,000 stillbirths.[2] 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 increase excitotoxic cellular damage leads to an accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which is then catabolized to adenosine, inosine and hypoxanthine.If there is uninterrupted tissue hypoxia and there is 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 come out in blood from tissues and excreted in urine.[3-7]

APGAR and umbilical cord blood pH are commonly used indicators for diagnosis and prognosis of birth asphyxia. The components of the APGAR score are subjective and depend on the maturity of the newborn.[8] The one-minute (1-min) APGAR score helped in assessing the need for immediate intervention; however, current guidelines recommend initiation of resuscitation in the event of neonatal depression. The five-minute (5min) APGAR score tells the effectiveness of resuscitation.[9] Exhaustive studies elucidating the mechanisms of tissue dam- age in birth asphyxia have been conducted but only few indicators like pH, lactate and base deficit have been studied. Not many studies on early markers of asphyxia and their relation to outcome are available. Markers like xanthine, hypoxanthine and inflammatory cytokines are not routinely done in laboratories.

We studied urine uric acid to creatinine ratio (UA/Cr), an easily accessible marker, in neonatal birth asphyxia.

**Correspondence*
Dr. Sujit Kumar Baranala
Senior Resident, Department of Pediatrics, Kalawati Saran Children Hospital, New Delhi, India.
E-mail: skbaranala2000@rediffmail.com

We also looked at its usefulness in the prognostication of the immediate outcome of these newborns.

Material and methods

This prospective observational study was carried out in the department of Department of Pediatrics, Kalawati Saran Children Hospital, New Delhi, India for one year. The urine samples from the 200 neonates comprising the cases and 200 neonates comprising the controls constituted the material for the study.

Inclusion criteria

- Gestational age ≥37weeks,
- Appropriate for gestational age,
- The neonates will be identified to have experienced perinatal asphyxia when at least 3 of the following are present,
- Apgar score of <7 at one minute of life,
- Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by Sarnat and Sarnat 19768.

Exclusion criteria

- Preterm /premature and IUGR babies,
- Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opiods (pharmacological depression),
- Maternal drug addiction,
- Hemolytic disease of the newborn,
- Neonates born to mothers on anti-epileptics,

Methodology

Detailed maternal history, assessment of intrauterine fetal wellbeing by continuous electronic fetal monitoring, meconium staining of amniotic fluid, birth events, Apgar score, sex of the baby and weight of the baby were recorded on the precoded proforma. Gestational age was assessed by New Ballard scoring system. Arterial blood gas analysis (ABG) was done for pH analysis, by collecting the cord blood sample, belonging to cases only, in the labour room itself. Thorough clinical and neurological examination was done for all the neonates included in the study. The asphyxiated neonates (case group) were monitored for seizures, hypotonia and HIE in the immediate neonatal period in the NICU.

Grading system used to grade the severity of HIE was SARNAT and SARNAT staging 1976 .[10] The cases were also observed for other systemic effects of asphyxia. Umbilical cord blood pH was done in all at birth and urine uric acid and urine creatinine within 24 hours of birth. Cord pH was estimated by the colorimetric method using the Cobas b 121 automated machine. Urine sample were collected from the newborns and sent for analysis. The spot urine samples were collected within 6-24 hours of life. The procedure was carried out using sterile urine collection bags, after which urine samples were frozen at - 20°C until analyses could be carried out. Uric acid and creatinine in single urine sample were determined by auto analyser,

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. Statistical test applied for the analysis was student t-test. The level of confidence interval and p-value were set at 95% and 5%.

Results

Table 1: Demographic data of study population

Parameters	Cases N=200 (%)	Controls N=200 (%)
Maternal risk factors		
Cephalopelvic disproportion	50 (25)	6 (3)
Maternal fever	29 (14.5)	5(2.5)
Pre-eclampsia	27 (13.5)	-
Diabetes Mellitus	9 (4.5)	-
Neonatal risk factors		
Late preterm	44 (22)	48 (24)
Meconium stained liquor	59 (29.5)	-
Neonatal sepsis	37 (18.5)	-
Mode of delivery		
Vaginal delivery	132 (66)	37(18.5)

Cesarean delivery	68(34)	163(81.5)
Type of positive pressure ventilation		
Bag and mask	167 (83.5)	-
Intubation	33(16.5)	-
Seizure	35 (17.5)	-
Death	15 (7.5)	-

Table 2: Encephalopathy staging of asphyxiated newborns

Encephalopathy	Case
None	153 (76.5)
Stage 1	11 (5.5)
Stage 2	11 (5.5)
Stage 3	25 (12.5)

Table 3: Apgar score further subdivided of neonates studied

Apgar score	Cases (n=200)		Controls (n=200)	
	No.	%	No.	%
Apgar score at 1min.				
0 - 3	180	90	0	0.0
4 - 6	20	10	0	0.0
≥7	0	0.0	100	100.0
Apgar score at 5min.				
0 - 3	34	17	0	0.0
4 - 6	58	29	0	0.0
≥7	108	54	100	100.0
Apgar score at 10min				
0 - 3	0	0.0	0	0.0
4 - 6	42	21	0	0.0
≥7	158	79	100	100.0

Table 4: Comparison of newborn asphyxia parameters

Parameter	Mean ± Standard Deviation		p-value*
	Control	Cases	
Urine,uric acid/creatinine	2.02± 0.71	3.01±1.37	0.011
Umbilical cord blood pH	7.29± 0.30	7.01±0.11	0.001

Test applied: t-test

Table 5: Urine uric acid/Creatinine ratio and umbilical cord blood pH according to the immediate outcome

Parameter	Mean ± Standard Deviation		p-value*
	Unfavorable outcome	Favorable Outcome	
Urine uric acid/creatinine	3.26±1.37	2.11±0.69	0.006
Umbilical cord blood pH	7.09±0.11	7.28±0.10	0.002

Discussion

The results of the present study showed that the urine UA/Cr was significantly different among the newborns with neonatal depression, birth asphyxia, and controls. A significant negative correlation between the ratio and the APGAR score and umbilical cord blood pH was also present.

The above study also found sex of the baby and birth weight of the neonate not to be statistically significant difference between the cases and control groups. But mode of delivery was found to be statistically significant in both studies with the cases group having statistically significant more number of caesarean sections. Also, the APGAR score at 1 minute, 5-minute, 10 minutes to statistically significant. Also, the APGAR score at 1 minute, 5-minute, 10 minutes to statistically significant between the case and the control group there by being helpful as an important tool for birth asphyxia diagnosis and its severity.

There were also significant differences of mean urinary UA/Cr ratio for Apgar score 4-6 vs Apgar score 0-3 ($p<0.001$) which is also similar 2 our study where apgar at 1min, 5min and 10min were found to be useful in diagnosis of asphyxia and its severity. The study conducted by LoftyM. El-Sayed et al. also reported that urinary uric acid to creatinine ratio in term and preterm infants was significantly higher in the asphyxia group than in non-asphyxiated group.[11]

There was also a significant difference based on the neonatal outcome with a threshold value. The mean difference of urine UA/Cr in the cases was compared with a few other studies. In the study by Kumar et al.[12] the mean urine UA/Cr was found to be statistically higher in asphyxiated babies (2.58 ± 1.09; $p<0.001$). However, this study did not determine the correlation between the urine UA/Cr and other asphyxia parameters or severity of asphyxia Basu et al.[13] showed a statistically significant higher urine UA/Cr in asphyxiated newborns (3.1 ± 1.3; $p<0.001$) as well as a significant negative correlation with the APGAR score ($r= -0.857$; $p <0.001$). Palit et al.[14] Study showed a moderate negative correlation between the ratio and umbilical cord blood pH ($r = -0.55$; $p<0.001$). There are not many studies that determine the utility of UA/Cr as a marker for the outcome. Choudhary et al.[15] proved a significant positive correlation between the urine UA/Cr and different stages of HIE classified according to Sarnat and Sarnat staging. Urine UA/Cr was significantly higher in severe HIE (3.61 ± 0.61) when compared to neonates with moderate HIE (2.95 ± 0.98) and mild HIE (2.64 ± 0.25) with a $p<0.001$.

Also in a study conducted by Pallab Basu et al., it was found that urinary UA/Cr ratio was significantly higher in cases than controls ($p<0.001$) which is similar to our study.[16] It was also found that there was significant difference between Apgar scores of cases than controls ($p= 0.02$).

Dong Wen Bin et al, in his study displayed that neonates who had been suffered from asphyxia have higher level of urinary uric acid to creatinine ratio as compared to the non-asphyxiated neonates. It may be used as an indicator for early assessment of aphyxial severity and also renal injury in post asphyxia neonates.[17]

Though APGAR at 1-min has been in use for decades, neonatal resuscitation is aimed at providing skilled care during the golden minute. We showed that there is an increasing trend in urine UA/Cr with birth asphyxia and negative correlation with cord pH which is the gold standard. A threshold value for immediate outcome was also obtained.To conclude urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia

Conclusion

The present study concludes that the urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia. This study opens new vistas for future research.

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