Urine Uric Acid Creatinine Ratio as a Diagnostic and Prognostic Marker of Neonatal Birth Asphyxia

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Abstract

Background: Cerebral hypoxia can result in anaerobic glycolysis which leads to decreased phosphorylase production and increased uric acid which gets excreted in the urine where it can be easily detected. The aim of the study is to assess the utility of urine uric acid creatinine ratio (UA/Cr) as an additional marker of neonatal depression and birth asphyxia and its utility as a potential prognostic indicator for the immediate outcome. **Subjects and Methods:** It was a case-control study that included 30 newborns born with an APGAR score of less than 7 at 1-min and requiring positive pressure ventilation. Cases were sub-grouped into neonatal depression and birth asphyxia. Newborns with moderate and severe encephalopathy were considered to have an unfavourable outcome. The urine UA/Cr was estimated in both groups. One-way Anova test, Spearman's rho and Receiver Operating Characteristic curve were used for statistical analysis. **Results:** The mean differences of urine UA/Cr were statistically significant (p=0.011) in birth asphyxia (3.02±1.34), neonatal depression (2.31±0.81) and controls (2.01±0.69). A significant negative correlation was seen with APGAR at 1-min (r=-0.43; p=0.001) and 5-min (r=-0.52; p=0.001) and umbilical cord blood pH (r= -0.29; p=0.021). The mean difference of UA/Cr between those with unfavorable (3.23±1.49) and favourable (2.14±0.73) outcomes was significant (p=0.006). A ratio ≥2.85 suggested the unfavourable outcome. **Conclusion:** The urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia.

Keywords: Apgar Score, Hypoxic-Ischemic Encephalopathy, Neonatal Depression, Umbilical Cord Blood pH

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Introduction

Neonatal depression is a descriptive term to describe any newborn showing a prolonged transition from intrauterine to extrauterine life. In contrast, birth asphyxia is a distinct term that identifies newborns with an impaired gas exchange or inadequate blood flow leading to persistent hypoxemia, hypercarbia and certain biochemical alterations.[1] Birth asphyxia is one of the major causes of neonatal morbidity and mortality. The incidence of birth asphyxia is 20 per 1000 births in developing countries, up to 10 times higher than in developed countries. Birth asphyxia is associated with mortality of 15-20% and morbidity of 25%.[2] The infant's brain is more vulnerable to hypoxic-ischemic injury as vaso-autoregulatory mechanisms are not well developed. In normal babies, oxygen and glucose are the main sources of energy. When cerebral hypoxia occurs, there is a decrease in glucose and Adenosine triphosphate (ATP) production due to anaerobic glycolysis.[3] Only two molecules of ATP are produced compared to thirty-two molecules of ATP during aerobic states. Also, phosphates are catabolized to adenosine, inosine, hypoxanthine and in the presence of xanthine oxidase, further to xanthine and uric acid. These metabolites enter the blood from damaged tissues and are excreted in the urine where they can be easily detected.[4,5]

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.[6] 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 (5-

min) APGAR score tells the effectiveness of resuscitation. [7] Exhaustive studies elucidating the mechanisms of tissue damage 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 depression and birth asphyxia. We also looked at its usefulness in the prognostication of the immediate outcome of these newborns.

Subjects and Methods

Design

It was a case-control study conducted at the Newborn and Birthing Units of Departments of Paediatrics and Obstetrics & Gynaecology of a teaching hospital between January 2018 and June 2019. The study included 30 newborns born with gestational age more than 35 weeks with APGAR score less than 7 at 1-min and requiring positive pressure ventilation as cases. Equal number of newborns matched for gestational age and who did not require resuscitation at birth were recruited as controls. Newborns with major congenital malformations, fetal growth restriction in the antenatal sonogram, small for gestational age babies and newborns born to mothers who received magnesium sulfate or opioids within four hours of labour were excluded in both the groups. The sample size was based on the study by Bhongir et al. [8] It was calculated using online software open-Epi (version 3.0) for 95% confidence interval (CI), 80% power, 1:1 ratio of cases and controls, for the calculated mean difference of 0.69 for urine UA/Cr.

The Institutional Ethical Committee clearance was obtained before the initiation of the study. Written informed consent was obtained from either of the parents.

Clinical data

The gestational age, maternal complications during pregnancy, drug history, mode of delivery, and meconium staining of amniotic fluid were recorded. APGAR score at 1-min and 5-min, details of resuscitation and birth weight were included. All newborns were followed up for the development of seizure and encephalopathy until discharge from the neonatal intensive care unit. The Sarnat and Sarnat classification was used for the staging of encephalopathy. [9]

Laboratory Analysis

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 uric acid (mg/dl) was estimated by

an enzymatic colorimetric method and urine creatinine (mg/dl) by buffered Jaffe's reaction using automated Cobas c 311.

Definitions

The following definitions were used in the study:

Neonatal depression was defined as any newborn requiring resuscitation with positive pressure ventilation at birth and umbilical cord blood pH >7. Birth asphyxia was a subgroup of the babies with depression at birth and APGAR score <7 at 5-min despite resuscitation or umbilical cord blood pH ≤7.0. The immediate outcome was considered as unfavorable when newborns had evidence of stages 2 (moderate) or 3 (severe) hypoxic-ischemic encephalopathy (HIE) according to Sarnat and Sarnat classification. [9]

Study Outcomes

The primary outcome was to see the utility of urine UA/Cr as a marker to identify birth asphyxia in newborns requiring resuscitation and whether it could be a prognostic indicator for the immediate outcome. The secondary outcome was to obtain a urine UA/Cr value that would indicate the unfavourable outcome.

Statistical Analysis

The software Statistical Package for Social Sciences version 22.0 (IBM SPSS, USA) was used for analysis. Demography data were expressed in frequency and percentage or median. The study group was divided into three: infants with neonatal depression, birth asphyxia and none. The Kolmogorov-Smirnov test was used to establish a normal distribution of cord pH and urine UA/Cr data across the three groups. A comparison of the mean difference between the groups was done by student t-test and ANOVA. Spearman's rho was used to determine the correlation between urine UA/Cr, APGAR, umbilical cord pH, and immediate neonatal outcome. The receiver operating characteristic curve (ROC) was used to determine the cut off value of urine UA/Cr for a favourable outcome that included control newborns. A p-value < 0.05 was considered statistically significant.

Results

[Table 1] gives the demography and risk factors for neonatal depression in the study population. Median gestational age in the cases and control groups was 39 weeks and 38 weeks respectively. The median birth weight in the case group (2990g) and the control group (3120 g) were comparable. Among the cases, 70% (n=21) had neonatal depression and 30% (n=9) had birth asphyxia. Comparison of mean differences of umbilical cord pH and mean differences of urine UA/Cr among the three groups were statistically significanc[Table 2]. A urine UA/Cr value of ≥2.63 distinguished neonatal depression and birth asphyxia with sensitivity of

Table 1: Demographic data of studypopulation.

Parameters	Cases n=30 (%)	Controls n=30 (%)
Maternal risk factors	7 (23.3)	1 (3.3)
Cephalopelvic disproportion	4 (13.3)	1 (3.3)
Maternal fever	4 (13.3)	-
Pre-eclampsia	1 (3.3)	-
Diabetes Mellitus		
Neonatal risk factors	6 (20.0)	6 (20.0)
Late preterm	8 (26.6)	-
Meconium stained liquor	5 (16.6)	-
Neonatal sepsis		
Mode of delivery	16 (53.3)	8 (26.6)
Vaginal delivery	9 (30.0)	22 (73.4)
Cesarean delivery	5 (16.6)	-
Assisted deliveries		
APGAR < 7 at 5-min	6 (20)	-
Type of positive pressure ventilation	24 (80)	-
Bag and mask	6 (20)	
Intubation		
Encephalopathy	22 (73.3)	-
None	2 (6.6)	-
Stage 1	2 (6.6)	-
Stage 2	4 (13.3)	
Stage 3	5 (16.6)	
Seizure	2 (6.6)	
Death		

Table 2: Comparison of newborn asphyxia parameters.

Parameter	Mean ± Standard deviation			p-value*
	Control	**Newborn depression**	**Birth asphyxia**	
Urine uric acid/creatinine	2.01± 0.69	2.31±0.81	3.02±1.34	0.011
Umbilical cord blood pH	7.32± 0.31	7.1±0.72	7.03±0.12	0.001

*ANOVA

Table 3: 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	3.23±1.49	2.14±0.73	0.006
Umbilical cord blood pH	7.11±0.13	7.25±0.11	0.002

*Independent sample t test

66.7% and 1-specificity of 23.8% {AUC=0.65[95% CI (0.42-0.88)]; p=0.197}. Urine UA/Cr showed a significant negative correlation with APGAR at 1-min (r= -0.43; p=0.001) and APGAR at 5-min (r= -0.52; p=0.001). Similarly, the ratio also showed a significant negative correlation with umbilical cord blood pH (r= -0.296; p=0.021). Among the newborns with neonatal depression (n=21), about 28.6% (n=2) had an unfavourable outcome. In newborns fulfilling criteria of birth asphyxia (n=9), nearly 71.4% (n=5) had an unfavourable outcome. [Table 3] shows that among the newborns with unfavorable and favorable outcomes, there was a statistically significant difference in mean urine UA/Cr and mean umbilical cord pH. The urine UA/Cr cut off of ≥2.85 had the best sensitivity (71.4%) and least false positivity (15.1%) for unfavorable outcome [AUC=0.74; 95% CI (0.50-0.98)] with p=0.040.

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. 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.[10] 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.[11] 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.[12] 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.[13] 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.

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 neonatal depression and birth asphyxia and negative correlation with cord pH which is the gold standard. A threshold value for immediate outcome was also obtained. These are some of the novelties of this study. Our study is a single centered study with limited sample size. Long term

outcome was not determined. To conclude urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia.

Conclusion

The urine UA/Cr is a useful diagnostic and prognostic biomarker in newborns with birth asphyxia.

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