Section: Miscellaneous

Original Research Article

URINARY URIC ACID AND CREATININE RATIO AS A MARKER OF NEONATAL ASPHYXIA FOR BABIES BORN IN A TERTIARY CARE HOSPITAL, SOUTH INDIA - A CASE CONTROL STUDY

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ABSTRACT

Background: Perinatal asphyxia is regarded as a major cause of avoidable brain injury. Birth asphyxia is responsible for 23% of all newborn fatalities worldwide. Despite growing understanding of the mechanisms that cause newborn hypoxia, early detection remains challenging. Hence this study was done with the objective to evaluate the utility of Urinary Uric Acid to Creatinine ratio (UUA/Cr ratio) within 24 hours of birth as non-invasive, early and reliable biochemical means of asphyxia diagnosis. **Materials and Methods:** This case-control study comprised 50 asphyxiated and 50 non-asphyxiated newborns based on APGAR scores, at a tertiary care hospital in South India between Oct-Dec 2023. UUA/Cr ratio was calculated from Spot urine samples collected within 24 hours. Grading for Hypoxic Ischemic Encephalopathy (HIE) was done using SARNAT and SARNAT staging. The analysis was conducted using appropriate statistical tests. **Result:** The mean UUA/Cr ratio was significantly elevated in cases (3.94±1.41) compared to controls (1.04±0.36). Additionally, the APGAR scores at 5 minutes were significantly lower in cases (7.18±1.22) compared to controls (8.68±0.51). Among cases, HIE 3 had highest UUA/Cr ratio (4.39±0.76). A one-way ANOVA revealed a significant difference between the groups [F (2, 47) =8.256,p =.001]. The cutoff value of the UUA/Cr ratio of 2.30 was 94% sensitive and 100% specific with Area Under Curve of 0.978 (p=<0.001). **Conclusion:** UUA/Cr ratio is an accessible, noninvasive, cost-effective method for predicting birth asphyxia at the earliest and thereby making it a valuable tool in deciding about the level of care needed by the newborn.

INTRODUCTION

Asphyxia (insufficient oxygen supply) is a common neonatal problem and contributes to significant morbidity and mortality in neonates. Asphyxia can lead to severe hypoxic-ischemic organ damage in newborns. Globally, birth asphyxia accounts for 23% of the million neonatal deaths each year.[1] In India, between 250,000 - 350,000 infants die each year due to birth asphyxia, mostly within the first three days of life.[2] According to the National Neonatal Perinatal Database (NNPD), birth asphyxia contributes to 8.4%, among them 1.4% suffer from Hypoxic Ischemic Encephalopathy (HIE), and 20% of neonatal deaths in India.[2] In a term infant with perinatal asphyxia, renal, neurologic, cardiac, and lung dysfunction occur in 50%, 28%, 25%, and 23% cases, respectively.[3] HIE is the foremost concern in asphyxiated neonates because, contrary to other system derangements, this has the potential to cause serious long-term neuro-motor sequelae among survivors.

During prolonged hypoxia, there is failure of oxidative phosphorylation and ATP production, sufficient to cause cellular damage. Subsequently, if there is uninterrupted tissue hypoxia and reperfusion injury, hypoxanthine is produced, which is oxidized to xanthine and uric acid, leading to increased uric acid production, which is excreted in urine.[4-6]

A variety of markers have been examined to identify perinatal hypoxia, including electronic fetal heart monitoring, low Apgar scores, cord blood PH, electroencephalograms (EEG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI) scans and Doppler flow studies. Though Apgar scores have historically been used to evaluate

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asphyxia as a diagnostic and prognostic index, their use is limited in predicting neurological outcome, which is influenced by various factors like immaturity, fetal malformations, maternal medications and infection.[7]

Previous studies have demonstrated higher cord blood hypoxanthine level concentrations in hypoxic fetuses.[8,9] Additional studies have indicated higher uric acid concentration in mothers with pre-eclampsia.[10,11]

Despite the increasing understanding of the mechanisms leading to and resulting from neonatal asphyxia, early determination of brain damage following hypoxic-ischemic events still remains the hardest problem in neonatal care.[12] Hence, this study is carried out with the following aims and objectives.

1. To evaluate the utility of urinary uric acid to creatinine ratio (UA/Cr ratio) within 24 hours of birth as a non-invasive, easy, cheap and at the same time early and reliable biochemical means of asphyxia diagnosis.
2. To correlate APGAR score with urinary uric acid to creatinine ratio in birth asphyxia.

MATERIALS AND METHODS

A hospital-based case-control study matched for gestational age was conducted among newborns delivered from October 2023 to December 2023 at a tertiary care hospital in South India. Ethical clearance was obtained from the hospital Ethics Committee. All newborns delivered during the data collection period were the source population. Study subjects were categorized into cases and controls based on APGAR score at 1 and 5 minutes. Those with APGAR scores of <7 at first and fifth minutes after delivery were defined as having birth asphyxia, while newborns with APGAR scores of >7 at first and fifth minutes as not having birth asphyxia.

The sample size was calculated with the formula for the matched case-control study with the ratio of controls to cases as 1:1, using the Mean ± Standard Deviation (SD) of 2.02±0.71 and 3.01±1.3713. With 95% confidence level and 80% power, the sample size was calculated to be 100 (50 cases and 50 controls) after adding 10% as a non-response rate and rounding off to the nearest whole number.

All newborns with birth asphyxia during the study period were included in the study and one control was selected for each birth asphyxia case. Newborns with Congenital malformations and those born to mothers having drug addiction, received magnesium sulphate within 4 hours before delivery or opioids (pharmacological depression), history of alcohol intake, smoking and antiepileptic treatment were excluded from the study.

A pre-tested and structured interviewer-administered questionnaire was used to collect maternal socio-demography and antepartum characteristics. Intrapartum and fetal characteristics data were extracted by using a pre-tested and structured checklist from the medical records of the women. The spot urinary sample was collected within 6-24 hrs. of life and sent for analysis for both controls and cases after informed consent from parents or caregivers. Both urinary uric acid and urinary creatinine were estimated by the kinetic method and the UA/Cr ratio was calculated. Complete clinical and neurological examination was done for all neonates included in the study. Cases were monitored for neurological complications due to perinatal hypoxia. Grading for HIE was done using SARNAT and SARNAT staging.

Data were entered into Excel and analysis was done using SPSS version 21.0. Continuous variables were summarized as mean and SD and Categorical variables were summarized as frequency and proportions. Student t test, ANOVA, Pearson correlation coefficient, and Chi-square test were applied to test the statistical significance.

RESULTS

The study included 50 cases (asphyxiated babies) and 50 controls who met the inclusion criteria and had a 100% response rate. The baseline maternal and fetal data were obtained, and the urinary uric acid and creatinine ratios were calculated for both cases and controls.

Table 1: Baseline characteristics of the study population (N=100)

Variables	n (%)	Case (n=50) n (%)	Control (n=50) n (%)	p value
Maternal characteristics				
Maternal age in years				
< 30	60 (60)	24 (48)	36 (72)	0.014*
≥ 30	40 (40)	26 (52)	14 (28)	
Working status				
Employed	31 (31)	21 (42)	10 (20)	0.545
Unemployed	69 (69)	29 (58)	40 (80)	
Gravida				
Primi	43 (43)	20 (40)	23 (46)	0.017*
Multi	57 (57)	30 (60)	27 (54)	
ANC visits				
1-3	8 (8)	8 (16)	0 (0)	0.003*
>3	92 (92)	42 (84)	50 (100)	
Mode of delivery				
Caesarean	55 (55)	28 (56)	27 (54)	0.841
vaginal delivery	45 (45)	22 (44)	23 (46)	

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Foetal characteristics				
Gender				
Male	67 (67)	34 (68)	33 (66)	0.832
Female	33 (33)	16 (32)	17 (34)	
Birth weight in kgs				
<2.5	27 (27)	14 (28)	13 (26)	0.822
≥2.5	73 (73)	36 (72)	37 (74)	
Gestational Age				
Term	88 (88)	6 (12)	6 (12)	1.000
Pre-term	12 (12)	44 (88)	44 (88)	
foetal presentation				
Vertex	96 (96)	46 (92)	50 (100)	0.041*
Breech	4 (4)	4 (8)	(0)	
Non-stress test				
Reactive	9 (9)	9 (18)	0 (0)	0.002*
Non-reactive	91 (91)	41 (82)	50 (100)	
Meconium-stained liquor				
Yes	12 (12)	12 (24)	0 (0)	<0.001*
No	88 (88)	38 (76)	50 (100)	
APGAR score at 5 min				
<7	13 (13)	13 (26)	0 (0)	<0.001*
≥7	87 (87)	37 (74)	50 (100)	

Note: *p value <0.05 is statistically significant.

Gestational age was matched between cases and controls. As shown in Table 1, baseline variables such as mode of delivery, gender, and birth weight of babies were similar in both groups. Breech presentation, ≤4 antenatal care (ANC) visits, meconium-stained liquor, reactive non-stress test, and APGAR score ≤7 at 5 minutes were seen only in cases. Less than one-third of the controls (28%) and more than half of the cases (52%) had mothers who were at least thirty years old. Unemployed mothers comprised 58% of cases and 80% of controls, whereas multigravida patients accounted for 60% of cases and 54% of controls. The study found a statistically significant association between several factors, including advanced maternal age, frequency of ANC visits, fetal presentation, meconium-stained liquor, non-stress test results, APGAR scores at 5 minutes, and the outcome of interest. These factors were found to be strongly associated with the outcome, suggesting a potential impact on the result.

Table 2: Comparison of APGAR score and UUA/Cr ratio among the study groups (N=100)

Variables	Category	Mean ± SD	Mean difference (95% CI)	Effect size (Cohen's D)	t	df	p value
UUA/Cr	Case (n=50)	3.94 ± 1.41	2.90 (2.48, 3.31)	2.82	14.08	55.52	<0.001*
	Control (n=50)	1.04 ± 0.36					
APGAR score at 5 min	Case (n=50)	7.18 ± 1.22	-1.50 (-1.88, -1.12)	-1.60	-7.98	65.68	<0.001*
	Control (n=50)	8.68 ± 0.51					

Note: *p value <0.05 is statistically significant.

The study revealed that the mean UUA/Cr ratio was significantly elevated in cases (3.94 ± 1.41) compared to controls (1.04 ± 0.36) with a large effect size (Cohen's D) of 2.82 indicating a substantial difference between the two groups. The mean difference of 2.90 suggests that cases are, on average, almost 3 units higher than controls. Additionally, the APGAR scores at 5 minutes were significantly lower in cases (7.18 ± 1.22) compared to controls (8.68 ± 0.51). The effect size (Cohen's d) is -1.60, which is a large effect size. This suggests that the difference between cases and controls is not only statistically significant but also practically meaningful. These findings indicate a notable difference in UUA/Cr ratios and APGAR scores between the two groups [Table 2].

Table 3: Correlation between APGAR score and UUA/Cr ratio of the study groups (N=100)

Variable	Mean ± SD	Pearson correlation	p-value
UUA/Cr	2.47 ± 1.67	-0.768	<0.001*
APGAR score at 1 min	5.35 ± 2.58		
UUA/Cr	2.47 ± 1.67	-0.534	<0.001*
APGAR score at 5 min	7.93 ± 1.20		

Note: *p value <0.05 is statistically significant.

A significant negative correlation exists between the UUA/Cr ratio and Apgar score at 1 and 5 minutes. [Table 3]

Table 4: Association between HIE and UUA/Cr ratio of the birth asphyxia group (N=50)

HIE Group	N	UUA/Cr Ratio Mean ± SD	ANOVA		
			df	F	Sig.
1	24	3.37 ± 1.00	2, 47	8.256	.001*
2	19	4.22 ± 1.07			

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3	7	4.96 ± 0.74				
Post Hoc test						
Dependent Variable: UUA/CR						
Tukey HSD						
(I) HIE	(J) HIE	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-0.85263*	.30860	0.022*	-1.599	-.105
	3	-1.59714*	.43169	0.002*	-2.641	-.552
2	1	0.85263*	.30860	0.022*	.105	1.599
	3	-0.74451	.44433	0.225	-1.819	.330
3	1	1.59714*	.43169	0.002*	.552	2.641
	2	0.74451	.44433	0.225	-.330	1.8199

Note: *p value <0.05 is statistically significant.

Among cases, HIE 3 had the highest UUA/Cr ratio (4.39 ± 0.76), followed by HIE 2 (4.27 ± 1.62) and HIE 1 (3.53 ± 1.29). A one-way ANOVA revealed a statistically significant difference between the groups (F (2, 47) = 8.256, p =.001). The Tukey post hoc test showed that HIE 3 (4.39 ± 0.76, p=0.002) and HIE 2 (4.27 ± 1.62, p=0.022) had substantially higher mean UUA/Cr ratios than HIE 1 (3.53 ± 1.29). The HIE 2 and HIE 3 showed no statistically significant difference (p =.225). [Table 4]

Table 5: ROC curve analysis of UUA/Cr ratio for predicting birth asphyxia (N=100)

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	Std error	p-value	95% CI of AUC
UUA/Cr Ratio	2.3	94	100	0.978	0.017	<0.001*	0.945, 1.000

Note: *p value <0.05 is statistically significant.

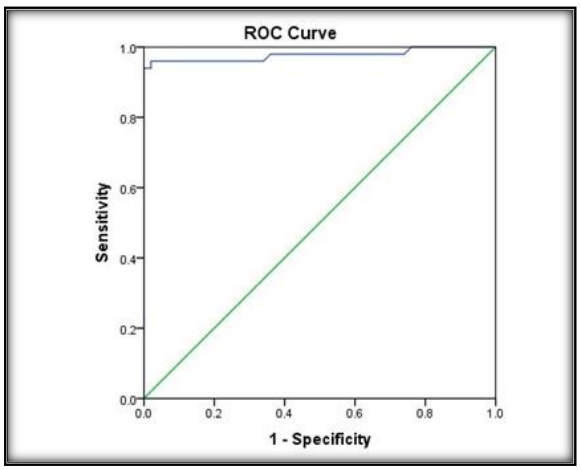

Figure 1: ROC curve

The cutoff value of the UUA/Cr ratio of 2.30 was found to be 94% sensitive, 100% specific. On plotting the ROC curve, the area under the curve was 0.978 (p <0.001) with a standard error of 0.017. [Table 5, Figure 1]

DISCUSSION

In this study, we investigated the utility of the urinary uric acid/creatinine (UUA/Cr) ratio as a predictor of birth asphyxia in neonates. The results showed a significant association between advanced maternal age, frequency of antenatal care visits, fetal presentation, meconium-stained liquor, non-stress test results, and APGAR scores at 5 minutes with birth asphyxia.

UUA/Cr appears as an early marker of hypoxic-ischemic brain injury. In our study, we observed a significantly higher UUA/Cr ratio in asphyxiated neonates (3.94 ± 1.41) than in the non-asphyxiated group (1.04 ± 0.36). Several studies have reported a similar association between UUA/Cr ratio in asphyxiated and non-asphyxiated neonates.[13-20] The APGAR scores at 5 minutes were significantly lower in cases (7.18 ± 1.22) compared to controls (8.68 ± 0.51) in our study. Basu et al,[16] and Reddy et al,[20] also reported significantly lower APGAR scores at 5 minutes in cases as compared to controls. There was a significant negative correlation of the UUA/Cr ratio with Apgar score at 1 and 5 minutes in our study. Basu et al,[16] and Arora et al,[14] also observed a significant negative correlation with APGAR score. Among cases, HIE 3 had the highest UUA/Cr ratio (4.96 ± 0.74), followed by HIE 2 (4.22 ± 1.07) and HIE 1 (3.37 ± 1.00), and it is statistically significant. Similar findings were reported by Arora et al,[14] and Chanpura et al.[21] The cutoff value of the UUA/Cr ratio in our study was found to be 2.30, and it is 94% sensitive, 100% specific, with a p value <0.001. Cutoff value close to our study was demonstrated by Reddy et al,[20] Bhongir et al,[22] and Patel et al.[23] Significantly lower cut-off values less than 2 were reported by Arora et al,[14] Choudhary et al,[15] and Akisu et al.[24]

CONCLUSION

Urinary UA/Cr ratio is an accessible, rapid, reliable, noninvasive, cost-effective method for predicting birth asphyxia at the earliest. It allows rapid recognition of asphyxia, assessment of its severity and the potential for short-term morbidity when performed on the earliest void urine sample, thereby making it a valuable tool in deciding about the level of care needed by the newborn.

Limitations: The fact that this study is single-center and has a tiny sample size limits our options. The predictive usefulness of this marker can be further enhanced by including more factors in multivariate

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analysis through multicentric studies with larger sample sizes.

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