

Usefulness of Urine Uric Acid/Creatinine Ratio in Neonate as an Early Detector of Perinatal Hypoxia: A Hospital-Based Observational Study**Saikat Mondal^a, Kanai Lal Barik^a, Sudipto Paul^a, Sumanta Laha^{a*}, Sayan Bera^a**^aDepartment of Pediatric Medicine, Burdwan Medical College, East Burdwan, West Bengal, India.**Abstract**

Background: When a neonate is born under a hypoxic state, there is increased production of uric acid due to hypoxic tissue damage, which is excreted via the kidney, and the ratio of uric acid and creatinine (UA/Cr) in urine is used as an early predictor of perinatal hypoxia.

Objectives: We conducted this study to compare urine UA/Cr ratio between normal and asphyxiated newborns and between different stages of HIE to evaluate its usefulness as a diagnostic and prognostic marker of perinatal asphyxia.

Patients and method: This observational cross-sectional study is conducted for one year with 75 asphyxiated neonates in different stages of HIE and 75 healthy neonates as control. Uric acid and creatinine values are measured with an auto-analyzer from a single urine sample taken between 6 to 24 hours of birth.

Results: We found urine UA (38 ± 2.81 mg/dl vs 19.24 ± 0.75 mg/dl) and urine UA/Cr value (2.81 ± 0.32 vs 1.40 ± 0.13) significantly high in cases compared to control. Also, the urine UA and UA/Cr values are increasing with advanced stages of HIE ($p < 0.001$). The optimal cut point value to predict HIE was at urine UA/Cr ratio of >2.45 with an AUC of 0.96, accuracy of 90%, sensitivity of 98.07%, specificity of 85.70%, PPV 78.46%, and NPV 98.82%.

Conclusion: Urine UA/Cr appears to be a simple, inexpensive and reliable indicator of perinatal hypoxia for risk stratification based on functional impairment in the HIE babies.

Keywords: Hypoxic Ischemic Encephalopathy; Neonate; Perinatal hypoxia; Uric Acid; Creatinine.

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Introduction

Perinatal hypoxia is among the major causes of newborn death and disability around the globe and also in South Asian countries like India. Perinatal hypoxia causes hypoxic cerebral damage which leads to encephalopathic changes known as Hypoxic Ischemic Encephalopathy (HIE). This HIE is responsible for both short-term poor prognosis like death and life-long disability like convulsion, cerebral palsy, visual and hearing problems, and other mental and neurological defects in survived neonates. It is found by multiple researchers have that brief hypoxia alters the oxidative metabolism in brain cells which causes an increase in anaerobic glycolysis, producing only two molecules of Adenosine Triphosphate (ATP), whereas 32 molecules of ATP are produced in an aerobic state (Patel et al., 2017).

Due to the persistence of tissue hypoxia, there is less production of ATP and more accumulation of Adenosine Monophosphate (AMP) and Adenosine Diphosphate (ADP), which are catabolized to its components of adenosine, inosine, and hypoxanthine. After the period of cellular hypoxia when tissue oxygenation is reestablished then there occurs reperfusion injury. This results in the production of xanthine and uric acid by the oxidation of hypoxanthine by the enzyme xanthine oxidase. Thus there is a surge in uric acid (UA) levels in asphyxiated babies that enter into the bloodstream from damaged cells and are ultimately excreted via the kidney to be easily detected in urine (Bhongir et al., 2015).

Urine Uric Acid/Creatinine ratio is a very easy, non-invasive, and

economical early biochemical marker to support a diagnosis of perinatal asphyxia (Gubbala et al., 2020). Though there are many studies across the world about using urine UA/Cr ratio as an early predictor of HIE, there is a lack of data from developing countries. This simple test is very easily done just with a spot urine sample and may detect perinatal asphyxia early where other expensive sophisticated tests are not available. So we performed our study to assess the utility of urine uric acid and creatinine ratio as a diagnostic and prognostic indicator of perinatal hypoxia in a peripheral medical college in West Bengal. Definite objectives of our study are; to find out any changes in urine uric acid creatinine ratio (UA /Cr ratio) in babies with perinatal hypoxia and HIE in comparison to normal newborns, and to assess any relation between urine UA/Cr ratio and grades of HIE.

Patients and methods

This hospital-based cross-sectional and observational Study was conducted in the Neonatal Intensive Care Unit (NICU) of Burdwan medical college and Hospital for one year. The study was conducted after obtaining informed and written consent from the parents of the neonates and necessary ethical clearance from the Institutional Ethics Committee (IEC) of Burdwan Medical College.

Taking the prevalence of perinatal asphyxia as 5.1% among live birth with a 95% confidence level and 5% allowable error our sample size calculated is at least 75 per group. In the study population, we included 75 neonates with perinatal asphyxia with

features of hypoxic-ischemic encephalopathy according to the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) criteria (1996). We have divided the neonates into HIE I, II, and III stages using the criteria of modified Sarnat and Sarnat HIE grading (**Sarnat and Sarnat, 1976**).

We used the below-mentioned inclusion and exclusion criteria before including our study subjects in the study group. Inclusion criteria are 1) gestational age of 37-42 weeks, 2) birth weight ≥ 2.5 kg, and 3) Age less than 24 hours. Exclusion criteria are 1) neonates with sepsis, 2) major congenital anomaly, 3) hemolytic disease and neonatal jaundice, 4) neonates who do not pass urine within 1st 24 hours of life or with compromised renal function.

Management of HIE was done according to the standard protocol. 75 healthy neonates are taken from the postnatal corner applying the same inclusion and exclusion criteria with similar gestational age and birth weight. Proper antenatal history and drug history were taken and detailed neonatal examination was done and neonatal screening for other associated conditions of hypoxic-ischemic encephalopathy like hypoglycemia, hypocalcemia, etc are performed. A spot urine sample was taken between 6-24 hours after birth. That was done by bladder stimulation technique with sterile urine collection bags, and the urine sample was kept at -20°C till the analysis was done. Uric acid and creatinine level in the same urine

sample was measured with the help of an auto analyzer.

Statistical analysis

The collected data are put into the Microsoft Excel worksheet (Microsoft, Redwoods, WA, USA) and necessary statistical analysis is done for comparison of values between groups using chi-square, student's t-test, Analysis of Variance (ANOVA) test, etc. All statistical tests are carried out using SPSS software, version 21.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA), and a p-value < 0.05 is taken as statistically significant. Receiver operator curve was constructed to evaluate the optimal UA/Cr ratio cutoff value in predicting the chance of HIE, and calculation of area under the curve, accuracy (Acc), sensitivity (Sn) and specificity (Sp), positive and negative predictive value. Calculations are done by the following formula ; $\text{Sn} = \text{TP} / (\text{TP} + \text{FN})$, $\text{Sp} = \text{TN} / (\text{TN} + \text{FP})$, $\text{PPV} = \text{TP} / (\text{TP} + \text{FP})$, $\text{NPP} = \text{TN} / (\text{TN} + \text{FN})$, $\text{Acc} = (\text{TP} + \text{TN}) / (\text{TP} + \text{TN} + \text{FP} + \text{FN})$, after taking true and false positive and negative cases from total 150 samples.

Results

In this study, we have measured Urine Uric acid, Creatinine, and Uric acid Creatinine ratio in 75 newborns with perinatal hypoxia with different stages of HIE and 75 healthy newborns with similar birth weight and gestational age. Among the 75 newborns in the study group, 23 (30.7%) were without HIE, 26 (34.7%) had mild HIE (stage I), 19 (25.3%) had moderate HIE

(stage II), and 7 (9.3%) had severe HIE (stage III) along their stay in NICU. Among 75 newborns of the

asphyxiated group, 66 (88%) were discharged, 7 (9.3%) leave against medical advice, and 2 (2.7%) died.

Table 1. Comparison of demographic and clinical data between two groups

Variables	Case (n=75)		Control (n=75)		P-value*
	No	%	No	%	
Gestational age 37-38 wks	08	10.7	10	13.3	0.577
▪ >38-40 wks	40	53.3	35	46.7	
▪ >40-42 wks	27	36	30	40	
Spontaneous vaginal delivery	41	54.7	46	61.3	0.588
Instrumental delivery	08	10.7	05	6.7	
Cesarean section	26	34.7	24	32	
Cephalic presentations	58	77.3	73	97.3	<0.001**
Breech presentations	14	18.7	02	2.7	
Shoulder presentations	03	4.0	00	00	
Newborn with neurological findings	43	57.3	00	00	<0.0001**
Newborn with seizure	31	41.3	00	00	<0.0001**

* Chi-squared test; ** Significant

(Table. 1) shows that gestational age and the mode of delivery were comparable in both groups (p=0.577 and 0.588 respectively). There is a significant difference in the presentation at delivery between the case and control groups

(p<0.001). Compared to the control group, 43(57.3%) of newborns had abnormal neurological findings (p <0.0001) and 31 (41.3%) newborns had a seizure in the cases group (p<0.0001).

Table 2. Variation of Urine Uric acid, Creatinine, and Uric acid Creatinine ratio between two groups

Variables	Case (n=75)		Control (n=75)		P-value*
	Mean	±SD	Mean	±SD	
Urine Uric Acid (UA) (mg/dl)	38.0	±2.81	19.24	±0.75	<0.001**
Urine Creatinine (Cr) (mg/dl)	13.62	±1.02	13.81	±1.25	0.06
Urine Uric acid Creatinine ratio (UA/Cr)	2.81	±0.32	1.40	±0.13	<0.001**

* Student's unpaired t-test; **Significant

(Table. 2) represents the comparison of urine uric acid, creatinine, and urineuric acid creatinine ratio between the case and control groups. The mean urine uric acid in the case and control group is 38 ±2.81

mg/dl and 19.24±0.75 mg/dl respectively. The urinary uric acid level is significantly high in the case group concerning the control group. Urinary creatinine level is almost the same in both groups with no significant difference (p=0.06). The mean urine

uric acid to creatinine ratio is 2.81±0.32 and 1.40±0.13 in the case and control groups respectively and

we found the ratio significantly high in the case group than its normal control (p <0.001).

Table 3. Variation of Urinary UA, Cr, and UA/Cr ratio between different stages of HIE in the case group

Variables	Perinatal asphyxia without HIE (n=23)	HIE			p-value*
		Stage I (n=26)	Stage II (n=19)	Stage III (n=7)	
Urine Uric Acid (UA) (mg/dl)	34.81±1.43	37.72±0.82	40.54±0.83	42.57±1.18	<0.001**
Urine Creatinine (Cr) (mg/dl)	13.78±0.95	13.69±0.93	13.42±1.09	13.35±1.21	0.619
Urine Uric acid to Creatinine ratio (UA/Cr)	2.53±0.21	2.77±0.21	3.04±0.24	3.22±0.21	<0.001**

*ANOVA test; **Significant

(Table .3) represents the correlation of urine uric acid, urine creatinine, and urine uric acid and creatinine ratio with HIE status among the asphyxiated neonates. It is seen that urine UA and UA/Cr ratio is higher in

advanced stages of HIE and the difference is statistically significant (p <0.001). However, urine creatinine shows no significant difference (p = 0.619).

Table 4. Sensitivity, Specificity, Predictive Value, and Accuracy of Urine UA/Cr >2.45 as a predictive marker of HIE

Urine UA/Cr	Sensitivity (Sn%)	Specificity (Sp%)	Positive Predictive Value (PPV%)	Negative Predictive Value (NPV%)	Accuracy (Acc%)	Area under the curve (AUC)
>2.45	98.07	85.70	78.46	98.82	90	0.96

From (Table .4 and Fig.1), we found that the optimal cut point value to predict HIE was at urine UA/Cr ratio >2.45 with an AUC

of 0.96, accuracy of 90%, sensitivity of 98.07% , specificity of 85.70% , PPV 78.46%, and NPV 98.82%.

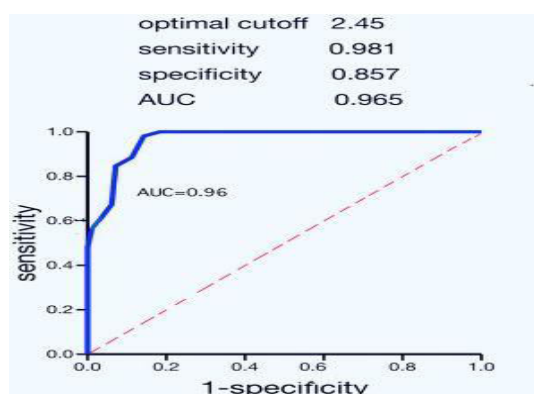


Fig 1: ROC curve for cut-off level of urine UA/Cr to predict HIE.

Discussion

Perinatal asphyxia leading to hypoxic-ischemic encephalopathy (HIE) is one of the leading causes of newborn death and long-term disability in different neonatal intensive care units in India. Different methods like fetal heart rate monitoring, APGAR scoring, cord blood pH measurement, and cranial MRI are used for early detection of perinatal hypoxia, but these methods are not without limitations and hence some easy methods for early identification of birth asphyxia and HIE is always a need. Different researchers assess different methods for early detection of hypoxic tissue damage in HIE neonates. In their study, **Basu et al., 2008**, showed that in asphyxiated newborns, the urine UA/Cr ratio in the first 24 hours of life was high compared to non-asphyxiated newborns (3.1 ± 1.3 vs. 0.96 ± 0.54 ; $p < 0.001$). A similar finding was shown in the studies conducted by **Bader et al., 1995**, and **Bhanupriya et al., 2008**.

During the state of cellular hypoxia and subsequent reperfusion injury after perinatal asphyxia, hypoxanthine is produced due to excess anaerobic glycolysis, which is then oxidized to xanthine and uric acid that is ultimately excreted in urine (**Bahubali et al., 2013**). Measurement of urine uric acid and creatinine ratio is a basic, non-invasive, economical, and easy-to-do test that uses spot urine samples. This simple test may be helpful, especially in a resource-limited country where more sophisticated tests are not always available. An increased UA/Cr ratio may serve as a useful marker

to detect the extent of cellular hypoxia in babies with perinatal asphyxia with normal renal functions. If renal function is compromised then this ratio will not help assess early tissue damage. In different research works urine uric acid and creatinine ratio served as an early marker of hypoxic-ischemic cerebral damage and a statistically significant high value had been observed in hypoxic newborns. Moreover, in the newborn with HIE, a significant correlation was seen between urine UA/Cr ratio and severity of encephalopathy ($P < 0.001$) (**Wen-Ben et al., 2002**; **Yashwanth et al., 2017**).

With this background, the present study is designed to assess the usefulness of urine uric acid/ creatinine ratio (UA/Cr ratio) as a non-invasive, simple, economical, and early biochemical marker of perinatal hypoxia and to find out the relationship between the level of urine UA/Cr ratio with different stages of HIE. Comparison of urine uric acid, creatinine, and urine uric acid creatinine ratio between the case and control group revealed that the mean urine uric acid in the case and control group was 38 ± 2.81 mg/dl and 19.24 ± 0.75 mg/dl respectively. We found urine uric acid levels significantly high in cases in comparison to the control. In terms of urinary creatinine level we found the mean level was 13.62 ± 1.02 mg/dl, and 13.81 ± 1.25 mg/dl in the case and control groups respectively without any significant difference ($p = 0.06$) and also indicating intact renal function. In the present work, the mean urine uric acid and creatinine ratio was 2.81 ± 0.32 and 1.40 ± 0.13 respectively in the case and

control groups. UUA/Cr ratio is high in the case group in comparison to normal newborns with a statistically significant difference ($p < 0.001$). Similar observations were published by **Sreekrishna et al., 2018**, where they reported urine UA/Cr ratios were significantly higher in the study group (HIE babies) than in controls (normal babies), (mean urine UA/Cr ratio was 2.8 ± 0.9 and 0.8 ± 0.2 ; $p < 0.001$ in case and control respectively), and **Choudhary et al., 2017**, where mean urine uric acid/creatinine ratio was 2.68 ± 1.06 in case group and 0.79 ± 0.36 in the control group ($p = 0.0001$).

Gubbala et al., 2020 in their work evaluated the urine Uric Acid/Creatinine ratio as an easy spot diagnostic test for early detection of perinatal hypoxia and reported that it was significantly higher in every asphyxiated newborn than in normal babies. The findings of our study are similar to the study by **Krishnana et al., 2017**, where they detected urine uric acid/creatinine value was significantly higher in hypoxic neonates than normal neonates ($0.78 - 4.94$ vs $0.42 - 1.96$) ($p < 0.001$).

In our research work, we found that urine UA and UA/Cr ratio is getting higher from stage I to stage III of HIE and the difference is statistically significant ($p < 0.001$). However, urine creatinine shows no significant difference ($p = 0.619$) between the three stages of HIE. **Choudhary et al., 2021** showed in their work, that a highly significant difference in urinary UA/Cr ratio was found from HIE stage I, stage II, and stage III. **Banupriya et al., 2008** also

showed Spearman's correlation demonstrating a significant positive correlation of urine UA/Cr value with HIE grading and a significant negative correlation with Apgar score. Equivalent results were documented by **Suman et al., 2019** where they found that the mean urine uric acid creatinine ratio in different grades of HIE showed a higher ratio with higher grades of HIE like high in grade II and III HIE (2.01 ± 0.42 & 4.24 ± 0.79) in comparison normal group (0.84 ± 0.56) and also concerning grade I HIE (1.23 ± 0.52) ($p < 0.0001$). **Choudhary et al., 2017**, found the same results in their study where they documented urine UA/Cr ratio of 3.61 ± 0.61 in severe HIE, 2.95 ± 0.98 in moderate HIE, and 2.64 ± 0.25 in mild HIE which is statistically significant ($p < 0.01$). **Gupta et al., 2020**, also showed an increasing trend of urine UA/Cr from mild to severe HIE.

In the present research work, the urine UA/Cr ratio of > 2.45 has 98.07% sensitivity, 85.70% specificity, 78.46% PPV, 98.82% NPV, with an AUC of 0.96 and 90% accuracy in diagnosing HIE. In their work, **Barder et al., 1995** found a positive predictive value of UUA/Cr of 78%, a negative predictive value of 72%, a sensitivity of 74%, and a specificity of 76% taking UUA/Cr value > 1.2 as a cut-off.

Conclusion

The urine UA/Cr ratio may serve as an easy, and simple screening tool for the early detection of perinatal hypoxia. It not only acts as an early marker of perinatal hypoxia but also helps to differentiate between mild asphyxia to

severe grades of HIE. Thus it can help both for early diagnosis and early initiation of treatment and also to assess prognosis as mortality and morbidity increase in advanced stages of HIE. So this simple test using spot urine samples can be utilized in low-resource settings for the early detection and management of perinatal hypoxia within 24 hours of birth.

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