International Journal of Contemporary Pediatrics
Chanpura VR et al. Int J Contemp Pediatr. 2022 Jun;9(6):584-588
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221378

Original Research Article

A study of urinary uric acid to creatinine ratio as a biochemical marker of perinatal asphyxia

Vaishali R. Chanpura*, Mayur G. Kacha

Department of Paediatrics, Medical College and SSG Hospital, Vadodara, Gujarat, India

Received: 07 April 2022
Revised: 04 May 2022
Accepted: 05 May 2022

***Correspondence:**
Dr. Vaishali R. Chanpura,
E-mail: chanpura92het@gmail.com

ABSTRACT

Background: Perinatal asphyxia remains an important cause of neonatal mortality, morbidity and sequelae especially in developing countries. Prevalence of perinatal asphyxia is 1 to 6 per 1000 live births while incidence of hypoxic-ischemic injury is 0.3 to 2 per 1000 term infants. There was a need to identify neonates with asphyxia at risk for hypoxic ischemic encephalopathy and multi-organ dysfunction using simple bedside tests. The objectives of the study were to evaluate the efficacy of uric acid to creatinine (UA/Cr) ratio in early spot urine samples as a diagnostic tool for perinatal asphyxia and to assess the relationship between urinary UA/Cr ratio and severity of HIE.
Methods: This study was conducted on 49 neonates having asphyxia (cases) and 49 neonates without asphyxia (controls) born at a tertiary care hospital over 12 months. Spot urine samples were collected within 24 hours of life and sent for analysis. A UA/Cr ratio of >2.51 was taken as cut-off value.
Results: The urinary UA/Cr ratio was found to be higher in asphyxiated infants (2.88±1.01) as compared to the control group (1.72±0.7, p<0.001). UUA/Cr ratio was significantly higher in infants with HIE stage 3 (3.65±1.4) as compared to infants with HIE stage 2 (2.62±0.76) and HIE stage 1 (2.71±0.4) (p<0.009). The cut-off UUA/Cr value of >2.51 has 71.43% sensitivity and 93.88% specificity.
Conclusions: The UUA/Cr ratio is a simple and reliable screening test for early diagnosis and assessment of perinatal asphyxia.

Keywords: Urinary uric acid/creatinine ratio, Hypoxic ischemic encephalopathy, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia continues to be the third most common cause of neonatal mortality in developing countries, and is responsible for 23% deaths. Approximately 4 million neonates suffer from birth asphyxia in a year.[1] Hypoxic-ischemic encephalopathy (HIE) is the neurological manifestation of systemic hypoxia in newborns. The clinical criteria of Sarnat and Sarnat measure the severity of HIE, classifying the patients in three stages according to level of consciousness, muscle tone, posture, tendon reflexes, presence or absence of myoclonus and change in autonomic functions.[2]

According to some researchers, 20-25% of asphyxiated babies who exhibit severe HIE die during the newborn period. Amongst babies who survive after severe HIE, up to 25% have permanent neuropsychological handicaps in the form of learning disabilities, epilepsy, cerebral palsy, with or without associated mental retardation.[4]

A clinician's ability to predict the outcome of neonates with HIE is not straightforward.

Routinely, APGAR score is used to evaluate asphyxia in neonates. But it cannot be used as a sole criterion to predict neurological outcome, because it is influenced by various factors like gestational age, cardio-respiratory malformations, anesthetic agents given to mother and intrauterine and perinatal infections.[3]

Cord blood pH and base deficit is considered the gold standard for defining asphyxia. However, it is not always feasible in resource poor settings.

In perinatal asphyxia, failure of oxidative phosphorylation and ATP production occurs as a consequence of prolonged hypoxia. Lack of ATP and increased cellular destruction cause an accumulation of adenosine monophosphate (AMP) and adenosine diphosphate (ADP), which then get catabolized to its constituents: adenosine, inosine and hypoxanthine.[6]

Continued tissue hypoxia and consequent reperfusion injury result in hypoxanthine being oxidized to xanthine and uric acid in presence of xanthine oxidase. This leads to increased uric acid production and its release into blood from damaged tissues. This uric acid then gets excreted in urine where it can be easily detected.[6]

This study will throw light on important role of urinary uric acid to creatinine ratio (UUA/Cr), for bedside use by clinicians in resource poor settings for diagnosis of perinatal asphyxia and stratify babies according to their severity. This will ensure that neonates are provided with specific therapy for asphyxia and are protected from exposure to unnecessary, ineffective therapies.

METHODS

This prospective case control study was conducted from December 2019 to November 2020 at a neonatal intensive care unit of department of pediatrics, SSG Hospital, a tertiary care center in western India after taking approval from institutional ethics and scientific committee.

The study population comprised of neonates born at obstetrics department of the hospital and referred from other centers for level III care. They were divided into case or control group based on presence of absence of birth asphyxia. The sample size was 98:49 cases and 49 controls.

The case group included 49 neonates fulfilling the following criteria: gestational age ≥37 weeks and presence of perinatal asphyxia defined by presence of at least one of the following: a) APGAR score of <7 at one minute of life, b) resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration. c) profound metabolic or mixed acidemia (pH<7.00) in an umbilical artery blood sample, if obtained.

Newborns having congenital malformations, maternal drug addiction, smoking or alcohol consumption during pregnancy, neonates born to mothers who received magnesium sulphate or opioids (pharmacological depression) within 4 hours prior to delivery, hemolytic disease of the newborn and neonates born to mothers on anti-epileptics were excluded from the study.

The control group included 49 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.

Written informed consent of parents/guardians was taken prior to starting study.

Neonates meeting inclusion criteria were enrolled in the study and managed as per NICU protocols. Detailed maternal history, perinatal events, APGAR score, sex and weight of the baby were recorded in the predesigned proforma.

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.[8] Grading system used to grade the severity of HIE was Sarnat and Sarnat staging 1976.[2] They were also observed for other systemic effects of asphyxia.

Neonates in control group were provided with routine newborn care.

Urine samples from neonates in both groups were collected and sent for analysis within 24 hours of life. The procedure was carried out using sterile urine collection bags, after which urine samples were frozen at -20°C until analysis could be carried out. Uric acid and creatinine in single urine sample were determined by auto analyser using enzymatic and colorimetric assays respectively.[9] Other relevant investigations including imaging studies were carried out in case group as part of management as well as to rule out causes of hypotonia, seizures, lethargy, poor feeding other than HIE.

Urinary uric acid and creatinine ratio was compared in both the groups. Correlation of this ratio with severity of HIE was done in case group.

Data was analysed in Microsoft excel with help of Med calc statistical software (licensed version). Statistical analysis of the data was performed using chi square test, ANOVA one-way test, unpaired t test with significance defined as p<0.05. Cut-off value of UUA/Cr ratio was obtained from ROC curve.

RESULTS

There was slight male preponderance in both case and control groups, but they were comparable to each other in gender distribution. Among 49 asphyxiated neonates in the case group 45 (91.8%) were term and 4 (8.16%) were post-term. In the control group 44 (89.8%) were term and 5 (10.2%) were post-term.

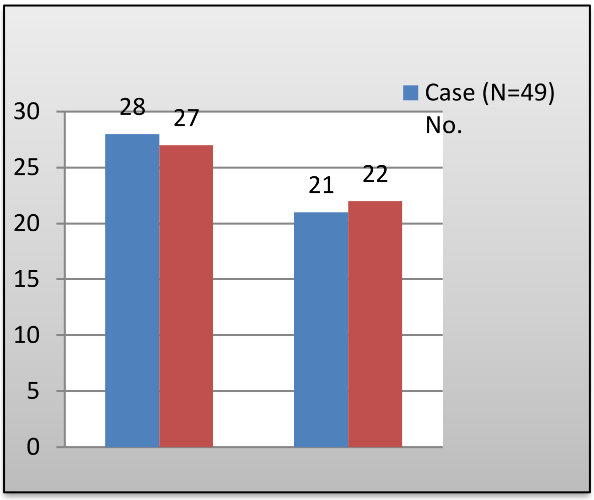

Figure 1: Gender distribution of study population.

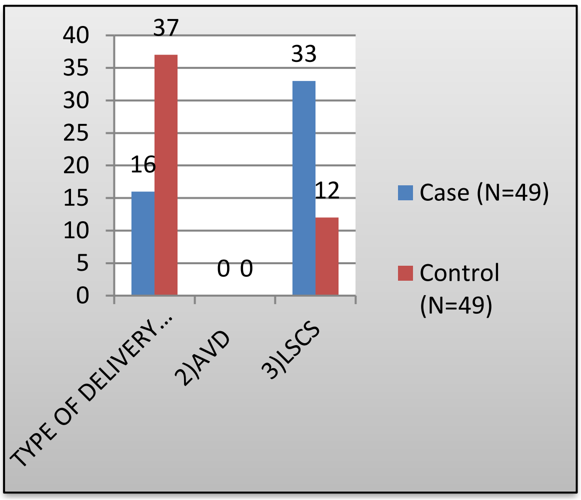

Figure 2: Mode of delivery.

Among the 49 neonates in case group, 16 (32.6%) neonates were delivered normally, 33 (67.35%) were delivered by caesarean section. Among the control group of 49 neonates, 37 (75.5%) were normal delivery, 12 (24.5%) neonates were delivered by caesarean section. The percentage of caesarean section was greater in the case group which can be explained by the fact that these newborns have foetal distress which necessitates emergency LSCS.

All the 49 (100%) neonates in the case group had an Apgar score of <7 at 1 minute, among them 5 (10.2%) had an Apgar score between 0-3 (severe birth asphyxia) and 44 (89.8%) had Apgar score between 4-6 (moderate birth asphyxia). At 5 minutes, 2 (4.08%) had an Apgar score between 0-3 and 42 (85.71%) had Apgar score between 4-6 remaining 5 (10.2%) cases had Apgar score of >7 at 5 minutes. All the neonates in control groups had Apgar score >7 at 1 minute and 5 minutes. The mean APGAR score of cases at 1 and 5 minutes were 5.1±1.18 and 6.39±1.32 respectively, while mean Apgar scores in controls were 8.37±0.47 and 9 respectively. All neonates in case group required resuscitation for >1 minute.

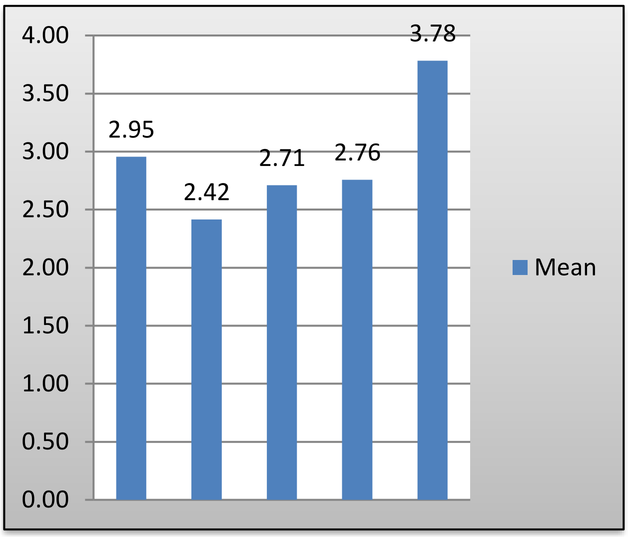

Figure 3: Relation of UUA/Cr ratio with stages of HIE.

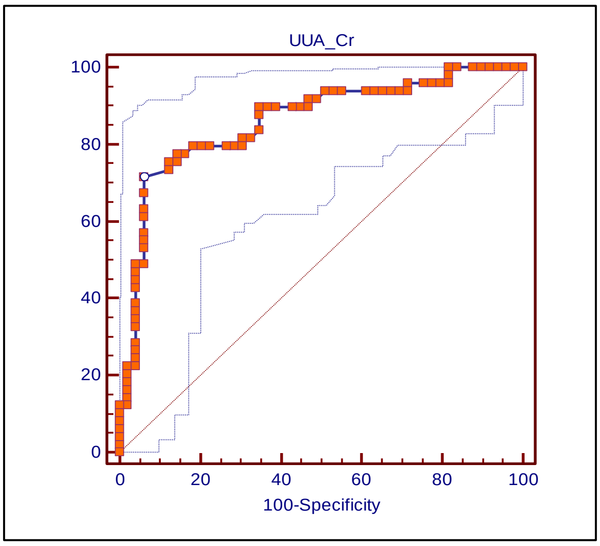

Figure 4: ROC curve for sensitivity and specificity of UUA/Cr ratio.

Among the 49 neonates in the case group, 9 (18.5%) had no HIE, 13 (26.5%) had mild HIE, 14 (28.5%) had moderate HIE and 13 (26.5%) had severe HIE. Seizures were present in 19 patients. About 50% of patients had hypotonia. In patients with severe HIE stages, significantly low mean Apgar scores were noted. The correlation of Apgar score at 1 min with HIE status among the cases was found to be statistically significant (p<0.001).

41 patients (83.6%) from group 1 were discharged while the rest succumbed; the mortality of birth asphyxia being 16.4%. All the neonates in group 2 were discharged.

Mean UUA/Cr ratio in case group was 2.88±1.01 whereas in control group it was 1.72±0.77 with a p<0.0001 which was statistically significant.

Further breakdown of UUA/Cr values amongst group 1 shows that neonates with no HIE had mean value of 2.4±0.7, HIE-1 had mean value of 2.7±0.4, HIE-2 had mean value of 2.6±0.7, HIE-3 had highest mean value of 3.65±1.4. P value was 0.001 which shows statistically significant correlation between UUA/Cr ratio and HIE stages.

Using ROC curves, the cut-off value of UUA/Cr was >2.51 with 71.43% sensitivity, 93.88% specificity, 69.23% positive predictive value and 76.7% negative predictive value, accuracy of 80% with p<0.001 which was statistically significant.

Table 1: APGAR score in cases and controls.

Apgar score	Case (n=49) Number	%	Control (n=49) Number	%
APGAR score at 1 min				
0-3	5	10.2	0	0.0
4-6	44	89.8	0	0.0
≥7.0	0	0.0	49	100.0
APGAR score at 5 min				
0-3	2	4.08	0	0.0
4-6	42	85.71	0	0.0
≥7.0	5	10.2	49	100.0

Table 2: Corelation of HIE stages with APGAR score.

APGAR score	Total number of patients (n=49)	HIE stage Normal (n=9)	Stage I (n=13)	Stage II (n=14)	Stage III (n=13)	P value
At 1 minute						
<7.0	49 (100.0%)	9 (18.5%)	13 (26.5%)	14 (28.5%)	13 (26.5%)	<0.0001
>7.0	0	0	0	0	0	
Mean±SD	5.1±1.18	6.1±0.6	5.69+-0.75	4.86±1.03	4.08±1.12	
At 5 minutes						
<7.0	19 (38.7%)	0 (0%)	2 (10.5%)	6 (31.5%)	11 (57.9%)	<0.0001
>7.0	30 (61.3%)	9 (30%)	11 (36.6%)	8 (26.7%)	2 (6.7%)	
Mean±SD	6.39±1.32	7.4±0.7	6.94±0.49	6.36±1.22	5.15±1.4	

Table 3: Statistically significant correlation of UUA/Cr.

UUA/Cr	Sensitivity	Specificity	PPV	NPV	Accuracy	Area Under ROC	P value
>2.51	71.43	93.88	69.23%	76.7%	80.00%	0.860	<0.001*

We could not carry out cord blood pH in any patient due to lack of bedside ABG machine. Within the first 24 hours, ABG could be done in 24 patients. Six neonates with HIE grade III had moderate acidosis and one neonate had mild acidosis. Even patients with moderate and severe encephalopathy did not have severe acidosis. We concluded that there was no significant correlation between pH and encephalopathy which might be due to the small sample size. Correlation between UUA/Cr ratio and ABG was not statistically significant.

DISCUSSION

This was a prospective case control study conducted over a period of 12 months from December 2019 to November 2020 at the neonatal unit of a tertiary care Government hospital.

There was a significant correlation between stages of HIE and Apgar score at one minute. This was similar to studies carried out by Ibrahim et al and Jones et al.[16,17] An article in the AAP journal says that Apgar score is a good tool to assess neonatal status at birth and is not very useful as a predictor of outcome.[2] Also, Apgar scores were not available in babies referred to tertiary care centres from other hospitals and hence cannot be used for neurological prognosis in such babies.

A study done by Saranaya et al was comparable with our study.[15] It showed mean UUA/Cr for cases were 2.59±1.04 among which neonates with no HIE had mean value of 1.28±0.3, HIE-1 had mean value of 2.66±0.7, HIE-2 had mean value of 2.79±0.74, HIE-3 had mean value of 4.29±0.46 which showed highest UUA/Cr ratio among HIE-3 patients. Bhongir et al and Patel et al also carried out similar studies in neonatal ICUs which showed significant difference in UUA/Cr ratio between normal and asphyxiated neonates.[5,13]

Study done by Krishna et al was comparable with our study in minimum and maximum value of UUA/Cr in all stages of HIE.[11] The cut-off value of the ratio (2.51) was close to that demonstrated by other studies like Patel et al and Aparna et al.[5] A study by El-Sayed et al proved that this ratio was 80% accurate, 76.6% sensitive, 83% specific; with a positive predictive value of 82.1% and negative predictive value of 78.1%.[14] These findings were corroborated by our study.

Limitations of the study

We could not carry out ABG analysis in all our patients due to lack of bedside ABG machine, therefore an important parameter of perinatal asphyxia could not be analysed. In the patients referred from other hospitals, exact APGAR score and perinatal events could not be documented and we relied on clinical signs for diagnosis of HIE.

CONCLUSION

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. 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. UA/Cr ratio estimation from spot urine sample is available at most centers and is a comparatively cheaper test. It allows rapid recognition of asphyxia, assessment of its severity and the potential for short term morbidity or death and can be used as a reliable, feasible, early screening test for assessment of perinatal asphyxia.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Eric EC, Anne HR, Cloherty. Cloherty and Stark manual of neonatal care. 8th ed. Eichenwald C Eric., editor. philadelphia: wolterkluwers. 686-7.
2. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographics study. Arch Neurol. 1976;33:696-20.
3. AAPCFN. The Apgar score. Pediatrics. 2006;117:1444-7.
4. Lawn JES, Cousens SZJ, Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? Lancet. 2005 365(9462):891-900.
5. Patel KP, Makadia MG, Patel VI, Nilayangode HNNS. Uric acid creat ratio as a marker of birth asphyxia. JCDR. 2017.
6. Manzke H, Kreudenstein PSV, Dorner K KK. Quantitative measurements of the urinary excretion of creatinine, uric acid, hypoxanthine and xanthine, uracil, cyclic AMP and cyclic GMP in healthy newborn infants. Eur J Pediatr. 1980;133:157-67.
7. Levene MI. Levene MI. The asphyxiated newborn infant. In: Levene MI, Lilford RJ, editors. Fetal and neonatal neurology and neurosurgery. 2nd edition. Edinburgh: Churchil Livingstone. 1995;405-26.
8. Agarwal R, Jain A, Deorari AK. Post-resuscitation management of asphyxiated neonates. Indian Journal of Pediatrics. 2008;75:175-80.
9. Kageyama N. A direct colorimetric determination of uric acid in serum and urine with uricase catalase system. Clin Chem Acta. 1971;31:421-6.
10. Basu P, Som S, Choudhuri N. Correlation between APGAR SCORE and urinary uric acid and creatinine ratio as a marker of Perinatal asphyxia. Indian Journal of Clinical Biochemistry. 2008;23(4)361-4.
11. Krishnana E, Ponnusamy V, Sekar SP. Study of urinary uric acid and creatinine ratio as a marker of neonatal asphyxia for babies born in a tertiary care hospital. Int J Res Med Sci. 2017;5(12):5418.
12. Bader BD, Weinger-Abend GDM, Berger A. neonatal urinary uric acid and creatinine ratio as additional marker of perinatal asphyxia. Eur J Pediatr. 1995;154:747-9.
13. Bhongir VA, Yakama VVA, Saha S, Radia SB, Pabbati J. The Urinary Uric Acid/Creatinine Ratio is An Adjuvant Marker for Perinatal Asphyxia Correspondence for. Eur J Pharm Med Res. 2015;2(5):520-8.
14. Lofty M, El-Sayed, Khater NM. Urinary uric acid and creatinine ratio and simkin’s index as marker of perinatal asphyxia. Zagazig University journal. 2001;2.
15. Saranaya SR, Rajamohan T. Study of urinary uric acid and creatinine as a marker for neonatal asphyxia IP. International Jouornal of Medical pediatrics and oncology. 2019;5(2)66-8.
16. Aliyu I, Lava TO, Onankpa B. Hypoxic ischaemic encephalopathyand the Apgar scoring system: The experience in a resource-limited setting. Journmal of clinical sciences. 2018;15:18-21.
17. Jones R, Heep A, Odd D. Biochemical and clinical predictors of hypoxic-ischaemic encephalopathy after perinatal asphyxia. J Matern Fetal Neonatal Med. 2018;31(6):791-6.

Cite this article as: Chanpura VR, Kacha MG. A study of urinary uric acid to creatinine ratio as a biochemical marker of perinatal asphyxia. Int J Contemp Pediatr 2022;9:584-8.