

## Original Research Article

DOI: <http://dx.doi.org/10.18203/2349-3291.ijcp20201500>

# Study of urinary uric acid and creatinine ratio as a marker for perinatal asphyxia

Trinadh Gubbala, Shree Krishna G. N.\*

Department of Paediatric, AJ Institute of Medical Science, Mangaluru, Karnataka, India

Received: 29 February 2020

Accepted: 23 March 2020

**\*Correspondence:**

Dr. Shree Krishna G.N.,

E-mail: shreekrishna\_gn@yahoo.co.in

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** Perinatal asphyxia refers to an impairment of the normal oxygenation during parturition and the ensuing adverse effects on the fetus/neonate. In India, due to birth asphyxia, between 250,000 to 350,000 infants die each year, mostly within the first three days of life. Low APGAR score is commonly used to as a indicator of asphyxia in infants, but it may often be not available and may be reduced in premature infants. In present study we evaluated urinary uric acid and creatinine ratio as a marker for perinatal asphyxia, at our tertiary care hospital.

**Methods:** Present study was a observational, case-control study, conducted in department of paediatrics, in case group consisted of 40 full-term neonates who were hospitalized with the diagnosis of perinatal asphyxia. The control group consisted of 40 healthy full-term newborns.

**Results:** Male to female ratio was 1.5:1 in case group as compared to 1.22:1 in control group. Mean gestational age in case group was  $286 \pm 10.32$  days, while in control group it was  $274 \pm 7.310$  days. Mean birth weight was  $2.72 \pm 0.51$  kg &  $2.88 \pm 0.49$  kg in case & control group respectively. In 52.5 % neonates from case group, signs of intrapartum fetal distress were noted. A statistically significant difference ( $p < 0.005$ ) was noted in Apgar 5 min, Arterial blood pH,  $pO_2$  (mm Hg),  $pCO_2$  (mm Hg), Urinary uric acid (mg/dl) and Urinary uric acid/ creatinine ratio. Authors did not noted any significant difference in Urinary creatinine (mg/dl) values of cases and control group. Urinary UA/CR ratio is significantly higher in case group when compared with control group with  $t = 11.19$ ;  $P < 0.001$ .

**Conclusions:** The ratio of urinary uric acid to creatinine helps in rapidly recognizing asphyxia and assessing its severity, so it can be a good, simple screening test for early assessment of neonatal asphyxia.

**Keywords:** APGAR score, Creatinine, Perinatal asphyxia, Urinary uric acid

## INTRODUCTION

Perinatal asphyxia refers to an impairment of the normal oxygenation during parturition and the ensuing adverse effects on the fetus/neonate. Cerebral blood flow and gas exchange is compromised in perinatal asphyxia leading to acidosis, hypercapnea and hypoxia.

In worldwide, birth asphyxia accounts for 26% of the 3.2 million stillbirths and 23% of the 4 million neonatal deaths each year.<sup>1</sup> Developing countries are more

effected 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.<sup>2</sup>

The outcomes of HIE (hypoxic ischemic encephalopathy) are devastating and permanent making it a major burden

for the patient, family and society. It is critical to identify and develop therapeutic strategies to reduce brain injury in newborns with asphyxia. Currently, despite the advances offered by therapeutic hypothermia in terms of neuroprotection, the improvements on long-term neurological outcome remain modest.<sup>3,4</sup>

Low APGAR score is commonly used to as an indicator of asphyxia in infants, but it may often be not available and may be reduced in premature infants. Other investigations that support the diagnosis of asphyxia are required to improve availability of therapy. pH values are quickly normalized after the onset of respiration, due to the elimination of carbon dioxide and cannot be relied upon in patients that are transported.<sup>5</sup>

Urinary UA/Cr ratio is simple, non-invasive, painless and economical investigation proposed for the diagnosis of perinatal asphyxia. In present study authors evaluated urinary uric acid and creatinine ratio as a marker for perinatal asphyxia, at our tertiary care hospital.

## METHODS

Present study was an observational, case-control study, conducted in department of paediatrics, AJ Institute of Medical Sciences. Study was performed during one-year period, from Sept 2018 to August 2019. Institutional ethical committee permission was taken for this study.

In study, case group consisted of 40 full-term neonates who were hospitalized with the diagnosis of perinatal asphyxia.

### Inclusion criteria

The diagnosis of asphyxia was confirmed if the infant met at least two of the following criteria:

- The presence of intrapartum fetal distress signs.
- Apgar score <6 at 5 minutes and/or pH <7.2 in the early postnatal blood gas determination.
- Need for neonatal resuscitation for more than one minute.

### Exclusion criteria

Babies with congenital malformations, suspected metabolic disease on treatment with diuretics, suffering from anuria and those born to mothers having hypertension, diabetes mellitus, toxæmia of pregnancy, receiving general anaesthesia, pethidine, phenobarbitone and other drugs likely to cause depression in babies.

The control group consisted of 40 healthy full-term newborns. Forty full-term healthy newborns in the control group were born after an uncomplicated pregnancy and had Apgar scores > 8 at 5 minutes and no signs of asphyxia. Attempts were taken to match case and control group parameters.

A written informed consent was taken from parents/guardians. The urine samples were collected in the first 24 hours of delivery and were frozen at -20°C until the time of analysis. Uric acid and creatinine in single urine samples by the uricase enzymatic kinetic methods. The results of the asphyxiated and control groups were compared in order to evaluate whether there was a significant difference in the uric acid/creatinine ratios between these groups.

Data was collected in a predesigned proforma and entered in Microsoft excel. Statistical analysis was done using descriptive statistics. Chi-square and Man-Whitney-U methods were used in the statistical evaluation of the data.

## RESULTS

In present study, 40 neonates were included in each case (asphyxiated) group and control group. Male to female ratio was 1.5:1 in case group as compared to 1.22:1 in control group. In case group post-dated (41-42 weeks) and post-term (> 42 weeks) neonates were also included. Mean gestational age in case group was 286±10.32 days, while in control group it was 274±7.310 days. Mean birth weight was 2.72±0.51 kg and 2.88±0.49 kg in case and control group respectively. In 52.5 % neonates from case group, signs of intrapartum fetal distress were noted. Mode of delivery (spontaneous vaginal, instrumental and caesarean section) was approximately same in both groups. (Table 1).

**Table 1: Demographic profile of cases and controls.**

Parameter	Cases	Controls
Gender		
Male	24	22
Female	16	18
Gestational Age		
Term	29	40
Post Dated	6	0
Post Term	5	0
Gestation (days) (mean±SD)	286±10.32	274±7.310
Birth Wt (Kg) (mean±SD)	2.72±0.51	2.88±0.49
<b>Intrapartum fetal distress signs</b>		
Present	21	0
Absent	19	0
Mode of delivery		
Spontaneous vaginal	22	25
Instrumental	04	3
Caesarean section	14	12

In control group all neonates had APGAR score more than 7. In cases group at 1 min, APGAR score of 0-3 and 4-7 was noted in 45% and 55% neonates respectively. After resuscitation at 5 min, APGAR score of 0-3, 4-7 and > 7 was noted in 17.5%, 37.5% and 45% neonates respectively. At 10 min, APGAR score of 4-7 and > 7

was noted in 22.5% and 77.5% neonates respectively (Table 2).

**Table 2: Apgar score of neonates.**

Apgar score	Cases		Control	
	No.	%	No.	%
<b>Apgar score at 1 min.</b>				
0 - 3	18	45	0	0
4 - 7	22	55	0	0
≥7	0	0	40	100
<b>Apgar score at 5 min.</b>				
0 - 3	7	17.5	0	0
4 - 7	15	37.5	0	0
≥7	18	45	40	100
<b>Apgar score at 10 min</b>				
0 - 3	0	0	0	0
4 - 7	9	22.5	0	0
≥7	31	77.5	40	100

Authors compared different parameters between case and control group. A statistically significant difference ( $p<0.005$ ) was noted in Apgar 5 min, Arterial blood pH,  $pO_2$  (mm Hg),  $pCO_2$  (mm Hg), Urinary uric acid (mg/dl) & Urinary uric acid/ creatinine ratio. We did not note any significant difference in Urinary creatinine (mg/dl) values of cases and control group. Urinary UA/CR ratio is significantly higher in case group when compared with control group with  $t=11.19$ ;  $P<0.001$  (Table 3).

**Table 3: Comparison of cases and control group.**

Parameter	Cases Group	Control Group	p-value
Apgar 5 min	5.62 (0.81)	8.29 (0.61)	$p<0.0001$
Arterial blood pH	7.06 (0.05)	7.41 (0.04)	$p<0.0001$
$pO_2$ (mm Hg)	39.21 (8.19)	57.98 (9.66)	$p<0.0001$
$pCO_2$ (mm Hg)	47.91 (4.71)	41.13 (3.17)	$p<0.0001$
Urinary uric acid (mg/dl)	39.88 (5.51)	19.91 (1.01)	$p<0.0001$
Urinary creatinine (mg/dl)	13.74 (2.03)	13.34 (3.21)	$p=0.5$
Urinary uric acid/ creatinine ratio	2.81 (0.31)	1.89 (0.19)	$p<0.0001$

Values expressed as Mean (SD)

## DISCUSSION

Birth asphyxia is largely recognized as the most frequent cause of acute interruption of oxygen to the fetus and the most common cause of brain damage.<sup>6</sup> Perinatal asphyxia is generally a clinical diagnosis based on recording of APGAR score at 1, 5 and 10 minutes of birth. Previously, many deliveries in India take place outside the medical

institutions and are unsupervised but contribute significantly to the total number of cases of perinatal asphyxia and HIE. In the absence of perinatal records it is very difficult to make a retrospective diagnosis of perinatal asphyxia and HIE due to overlapping signs and symptoms like hypotonia, lethargy, refusal to feed and seizures which may be due to various other causes. Despite the increasing understanding of the mechanisms leading to and resulting from perinatal asphyxia, early determination of brain damage following hypoxic-ischemic events still remains one of the hardest problems in neonatal care.

Apgar score alone does not predict neurologic outcome like cerebral palsy and as it is influenced by various factors like immaturity, fetal malformations, maternal medications and infection. Retrospective diagnosis of birth asphyxia is very difficult due to overlap of symptoms of perinatal asphyxia with various other conditions in the newborn. Umbilical cord ABG estimation may also help in diagnosis of asphyxia if carried out in half an hour of birth but most of the time neonates present much later than half an hour. Studies conducted for the outcomes of children with acute perinatal asphyxia and/or neonatal encephalopathy have noted that among children with moderate encephalopathy the disability rate ranges from 6-21% and among children with severe encephalopathy ranges from 42-100%.<sup>7</sup>

To identify the perinatal asphyxia, many markers have been examined including low APGAR scores, cord pH, computed tomography (CT), electroencephalograms (EEG) and magnetic resonance imaging (MRI) scans and Doppler flow studies.

Prolonged hypoxia in newborn baby causes decrease in cardiac output which leads to the compromised cerebral blood flow and with combined hypoxic ischemic insult produces failure of ATP production with accumulation of ADP and AMP. Catabolism of these products leads to increase uric acid production with increased urinary excretion. Hypoxic ischemic events and inflammatory processes can cause renal damage, which leads to urinary uric acid excretion, which is a product of purine catabolism and free radicals due to the activation of xanthine oxidase. This will increase the production of uric acid and cause it to enter blood from damaged tissues. This uric acid will then get excreted in urine where it can be easily detected. urinary Uric Acid/Creatine ratio is simple, non-invasive, painless and economical investigation for the diagnosis of perinatal asphyxia. Combined use of arterial blood pH, Apgar scores and urinary Uric Acid/Creatine ratio can help in early decision making about the level of care the new born requires.

Present study evaluated the urinary Uric Acid/Creatine ratio as a single, simple test for diagnosis of asphyxia and shows that it was elevated in all preterm neonates who were admitted, in comparison with healthy infants who

were born in our hospital. Chen et al.<sup>8</sup> reported that the urinary Uric Acid/Creatine ratio was remarkably higher in hypoxic premature infants than in hypoxic term infants.<sup>8</sup> Bahubali et al, reported that this ratio was elevated in neonates with birth asphyxia compared with the control group, and that this ratio was correlated significantly with the clinical severity of the disease.<sup>9</sup>

Vandana et al., concluded in their study that the Urinary uric acid and creatinine ratio was significantly higher ( $P<0.0001$ ) in asphyxiated babies ( $3.02\pm1.26$ ) compared to control group ( $0.84\pm0.56$ ).<sup>10</sup> Mean values of urinary uric acid creatinine ratio in different stages of HIE showed increasing ratio with increasing stages of HIE with significantly higher ratios ( $p<0.0001$ ) in stage II and III HIE ( $2.01\pm0.42$  and  $4.24\pm0.79$ ) compared to control group ( $0.84\pm0.56$ ) and also compared to stage I HIE ( $1.23\pm0.52$ ) ( $p<0.0001$ ).

pH, lactates and base deficits can also use to diagnose birth asphyxia. But pH, lactates and base deficits subside with the establishment of respiration, and with other mode of resuscitation. Also, pH, lactate, base deficit estimations are invasive and require sophisticated instruments, but urinary uric acid/ creatinine ratio is simple, cost effective, non-invasive and early biochemical means of asphyxia diagnosis.

Studies also reported a significant negative correlation between Urinary Uric Acid/Creatine Ratio and the Apgar score, noted in studies by Banupriya C et al, and Bhongir Aparna.<sup>11,12</sup> In the results from the study by Banupriya, C et al, the Spearman's correlation depicts that urine uric acid: creatinine ratio show a significant positive correlation with HIE staging and significant negative correlation with APGAR score.

## CONCLUSION

The ratio of urinary uric acid to creatinine helps in rapidly recognizing asphyxia and assessing its severity, so it can be a good, simple screening test for early assessment of neonatal asphyxia. Further research is needed to establish a correlation between urinary uric acid/creatinine ratio and the severity of encephalopathy.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? *Lancet.* 2005;365(9462):891-900.

2. Network NN. National Neonatal-Perinatal Database (Report 2002–2003). New Delhi, India: Department of Pediatrics, All India Institute of Medical Sciences. 2005. Available at: [https://www.newbornwhocc.org/pdf/nnpd\\_report\\_2002-03.PDF](https://www.newbornwhocc.org/pdf/nnpd_report_2002-03.PDF)
3. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM et al., Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet.* 2005;365(9460):663-70.
4. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, Donovan EF, Fanaroff AA et al., Wholebody hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Eng J Med.* 2005;353(15):1574-84.
5. American Academy of Pediatrics. The APGAR score. *Adv Neonatal Care.* 2006;6(4):220-3.
6. Bracci R, Perrone S, G. Buonocore G, The timing of neonatal brain damage. *Neonatology.* 2006;90(3):145-55.
7. Odd DE, Whitelaw A, Gunnell D, Lewis G. The association between birth condition and neuropsychological functioning and educational attainment at school age: a cohort study. *Arch Dis Child.* 2011;96:30-7.
8. Chen HJ, Yau KI, Tsai KS. Urinary uric acid/creatinine ratio as an additional marker of perinatal asphyxia. *J Formos Med Assoc.* 2000;99(10):771-4.
9. Bahubali DG, Bhat VB, Ramachandra R, Adhisivam B, Rojo J, Prasad P, et al. Biochemical marker as predictor of outcome in perinatal asphyxia. *Cur Ped Res.* 2013;17(2).
10. Vandana V, Amit V, Meena V, Anuradha B, Vivek B, Deepak V, et al. Study of basic biochemical and haematological parameters in perinatal asphyxia and its correlation with Hypoxic ischemic encephalopathy staging. *J Adv Res Bio Sci.* 2011;3(2):79-85.
11. Banupriya C, Doureradjou P, Mondal N, Vishnu B, Koner BC. Can urinary excretion rate of malondialdehyde, uric acid and protein predict the severity and impending death in perinatal asphyxia?. *Clin Biochem.* 2008;41(12):968-73.
12. Bhongir AV, Yakama AV, Saha S, Radia SB, Pabbati J. The Urinary Uric Acid/Creatinine Ratio is An Adjuvant Marker for Perinatal Asphyxia. *Eur J Pharm Med Res.* 2015;2(5):520-8.

**Cite this article as:** Gubbala T, Krishna SGN. Study of urinary uric acid and creatinine ratio as a marker for perinatal asphyxia. *Int J Contemp Pediatr* 2020;7:993-6.