

## Original Research Article

# Study of urinary uric acid and creatinine ratio as a marker of neonatal asphyxia for babies born in a tertiary care hospital

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**Received:** 15 October 2017

**Accepted:** 11 November 2017

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### ABSTRACT

**Background:** Perinatal asphyxia is a common neonatal problem and there is significant contribution to neonatal morbidity and mortality. It is regarded as an important and common cause of preventable cerebral injury. The prediction of perinatal asphyxial outcome is important but formidable. There is only a limited role for the Apgar score for predicting the immediate outcome, such as HIE and the long-term neurological sequelae observational error can happen in APGAR. But biochemical parameters can be truly relied upon. This study was to evaluate the utility of urinary uric acid to creatinine ratio (UA/CR ratio) as non-invasive, easy, cheap and at the same time early biochemical means of asphyxia diagnosis.

**Methods:** In this prospective case control study conducted in KAPV Government medical college between Feb 2017 to Sept 2017, 100 asphyxiated and 100 non-asphyxiated newborns were included. Detailed history and assessment were for all the enrolled newborns. Spot urine samples were sent for uric acid and creatinine estimation. Results were recorded, and statistical analysis was done.

**Results:** The mean Uric acid/Creatinine ratio in the cases and controls groups were  $2.58 \pm 1.09$  and  $0.86 \pm 0.17$  respectively. The ratio also correlated well with the stage of HIE.

**Conclusions:** The ratio of UA/Cr enables early and rapid recognition of asphyxial injury and also the assessment of its severity and the potential for short term morbidity or death.

**Keywords:** Creatinine, HIE, Perinatal asphyxia, Uric acid

### INTRODUCTION

Perinatal asphyxia is a common neonatal problem and there is significant contribution to neonatal morbidity and mortality. 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.<sup>2</sup> Perinatal asphyxia contributes to almost 20% of neonatal deaths in India as per the data by National Neonatal Perinatal database (NNPD).<sup>2</sup> The

contribution of ante-partum and intra-partum asphyxia are about 300,000 to 400,000 stillbirths.<sup>2</sup> During prolonged hypoxia, cardiac output falls, cerebral blood flow (CBF) is compromised and a combined hypoxic-ischemic insult produces further failure of oxidative phosphorylation and ATP production, sufficient to cause cellular damage. Lack of ATP and increase excitotoxic cellular damage leads to an accumulation of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which is then catabolized to adenosine, inosine and hypoxanthine.<sup>3-7</sup>

If there is uninterrupted tissue hypoxia and there is also reperfusion injury, hypoxanthine is oxidized to xanthine

and uric acid in presence of xanthine oxidase leading to an increase in uric acid production, which come out in blood from tissues and excreted in urine.<sup>3-7</sup>

This study was to evaluate the utility of urinary uric acid to creatinine ratio (UA/Cr ratio) as non-invasive, easy, cheap and at the same time early biochemical means of asphyxia diagnosis and also to find out whether Apgar score is still an important tool for birth asphyxia diagnosis and its severity.

## METHODS

Study design: Prospective case control study. Study place: NICU unit, KAPV Government medical college. Study period: Feb 2017 to Sept 2017 (8months).

Study population: Cases and Controls comprised of asphyxiated and non-asphyxiated neonates, respectively. The urine samples from the 100 neonates comprising the cases and 100 neonates comprising the controls constituted the material for the study.

Method of collection of data: The study included two groups.

### Inclusion criteria

- Gestational age  $\geq 37$  weeks,
- Appropriate for gestational age,
- The neonates will be identified to have experienced perinatal asphyxia when at least 3 of the following are present,
  - Intrapartum signs of fetal distress, as indicated by non-reassuring NST on continuous electronic fetal monitoring and/ or by thick meconium staining of the amniotic fluid,
  - Apgar score of  $< 7$  at one minute of life,
  - Resuscitation with  $> 1$  minute of positive pressure ventilation before stable spontaneous respiration.
  - Fetal H.R  $< 60$  beats/min,
  - Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by Sarnat and Sarnat 1976.

### Exclusion criteria

- Congenital malformations,
- Preterm /premature and IUGR babies,
- Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opioids (pharmacological depression),
- Maternal drug addiction,
- Hemolytic disease of the newborn,
- Neonates born to mothers on anti-epileptics,
- Mothers having hypertension/ diabetes mellitus, toxemia of pregnancy,
- Neonates born to mothers on smoking/ alcohol.

### The control groups

It included 100 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  $\geq 7$ . All neonates included in the study had the following done

- Detailed maternal history, assessment of intrauterine fetal wellbeing by continuous electronic fetal monitoring, meconium staining of amniotic fluid, birth events, Apgar score, sex of the baby and weight of the baby were recorded on the precoded proforma. Gestational age was assessed by New Ballard scoring system. Arterial blood gas analysis (ABG) was done for pH analysis, by collecting the cord blood sample, belonging to cases only, in the labour room itself. Due to non-availability of the sources for some period of time during the study period, ABG has been done for only 50 cases, without any selection bias. For controls, ABG has not been done,
- 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. Grading system used to grade the severity of HIE was SARNAT and SARNAT staging 1976.8 The cases were also observed for other systemic effects of asphyxia,
- Urine sample were collected from the newborns and sent for analysis. The spot urine samples were collected within 6-24 hours of life. The procedure was carried out using sterile urine collection bags, after which urine samples were frozen at  $- 20^{\circ}\text{C}$  until analyses could be carried out. Uric acid and creatinine in single urine sample were determined by auto analyser,
- The case group also had other investigations and imaging studies done as required for post-resuscitation management of asphyxiated neonates. The causes for hypotonia, seizures, lethargy, poor feeding other than HIE were ruled out with relevant investigations available. Statistical analysis was done.

## RESULTS

Among the 100 neonates in case group, there were 58 (58%) males and 42 (42%) females. Among the control group of 100 neonates, there were 50 (50%) males and 50 (50%) females.

Among the case group 62 (62%) were term gestation, 28 (28%) were postdated and 10 (10%) were post term according to gestation whereas all normal neonates which constituted the control group were term gestationally. 78 (78%) neonates weighed between 2.5-3.0kg, 14 (14%) weighed between 3.0-3.5kg and 8 (8%) weighed  $> 3.5$ kg in case group.

Among the control group of 100 neonates, 60 (60%) neonates weighed between 2.5-3.0kg, 28 (28%) weighed between 3.0-3.5kg and 12 (12%) weighed >3.5kg. The mean weight in case group was 2.92±0.36 kg and in control group was 3.02±0.38kg.

Sex, gestational age and birth weight were matched between the cases and controls. Among the 100 neonates in case group, 54 (54%) were born to primi mothers and 46 (46%) were born to multi gravida mothers.

Among the control group of 100 neonates, 52 (52%) were born to primi mothers and 48 (48%) were born to multigravida mothers. Proportion of primi and multi gravid mothers are statistically similar with P=0.057.

Among the 100 neonates in case group, 54 (54%) neonates were delivered normally, 36 (36%) were delivered by caesarean section and 10 (10%) had instrumental delivery.

Among the control group of 100 neonates, 96 (96%) had normal delivery, 2 (2%) neonates were delivered by caesarean section and none had instrumental delivery. Incidence of caesarean section and instrumental delivery are significantly more in case group (88%) compared to control group (34%) with P<0.001.

**Table 1: Signs of fetal distress of newborns studied.**

Fetal distress	Cases(n=100)		Controls(n=100)	
	No.	%	No.	%
<b>Non-stress test</b>				
Reactive	12	12.0	100	100.0
Non-reactive	88	88.0	0	0.0
<b>Thick MSAF</b>				
Negative	56	56.0	100	100.0
Positive	44	44.0	0	0.0

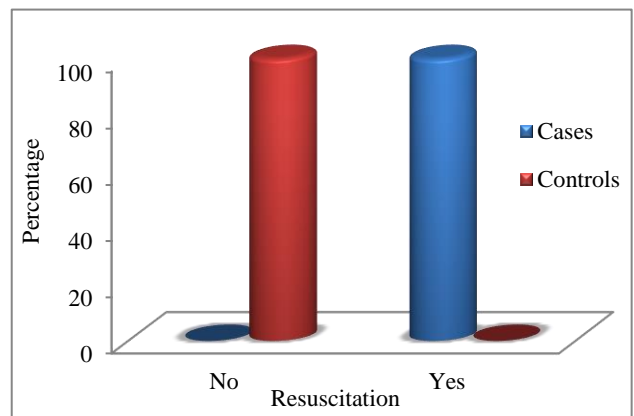
Among the 100 neonates in case group, 90 (90%) neonates had cephalic presentation, 8 (8%) had breech presentation, 2 (2%) had shoulder presentation and non-had brow presentation.

Among the control group of 100 neonates, 96 (96%) had cephalic presentation, 4 (4%) neonates had breech presentation, and none had shoulder or brow presentation. The cases and control group were statistically similar with P=0.658. Incidence of non-reassuring NST and thick MSAF were significantly more in case group (78.0%) against control group. Incidence of Apgar score <7 is significantly more in cases (100.0%) at 1 min and 5 min with P<0.001 (Table 2).

Among the 100 neonates in case group, all the 100 (100%) neonates were in need of resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration. All the 100 (100%) neonates in control group were not in need of any such intervention cases (100.0%) with a P<0.001 (Figure 1).

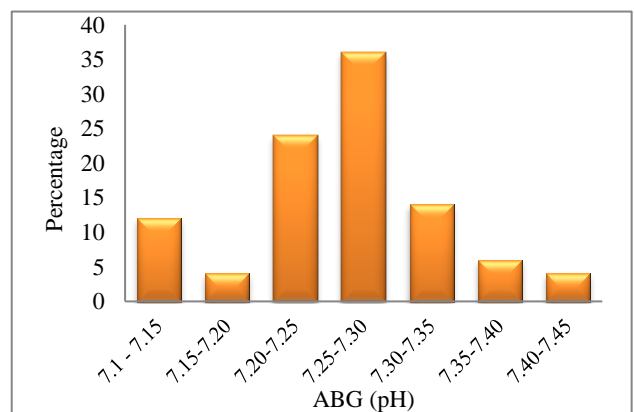
**Table 2: Apgar score further subdivided of neonates studied.**

Apgar score	Cases(n=100)		Controls(n=100)	
	No.	%	No.	%
<b>Apgar score at 1min.</b>				
0 - 3	88	88.0	0	0.0
4 - 6	12	12.0	0	0.0
≥7	0	0.0	100	100.0
<b>Apgar score at 5min.</b>				
0 - 3	16	16.0	0	0.0
4 - 6	32	32.0	0	0.0
≥7	52	52.0	100	100.0
<b>Apgar score at 10min</b>				
0 - 3	0	0.0	0	0.0
4 - 6	24	24.0	0	0.0
≥7	76	76.0	100	100.0



**Figure 1: Resuscitation of newborns studied.**

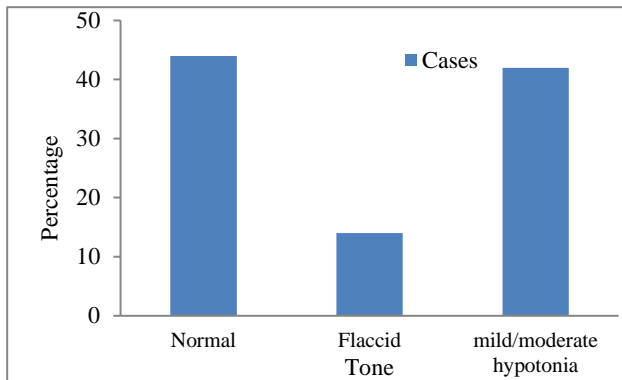
Out of the 100 cases of neonatal asphyxia studied 6 (12%) of the neonates had arterial pH between 7.1-7.15, 2 (4%) of the neonates had arterial pH between 7.15-7.2, 12 (24%) of the neonates had arterial pH between 7.2-7.25, 18 (36%) of the neonates had arterial pH between 7.25-7.3, 7 (14%) of the neonates had arterial pH between 7.3-7.35, 3 (6%) of the neonates had arterial pH between 7.35-7.4, 2 (4%) of the neonates had arterial pH between 7.4-7.45 (Figure 2).



**Figure 2: Cord blood Ph of newborns studied.**

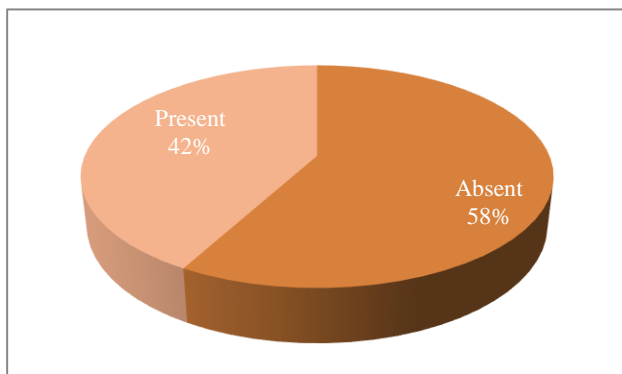
Among the 100 neonates in case group, 44 (44%) had normal neurological examination with normal tone. 42 (42%) had mild and marked hypotonia and 14 (14%) were flaccid with severe hypotonia. All the 50 (100%) neonates in control group had normal neurological examination.

Abnormal neurological examination is significantly more (56.0%) in cases when compared to Controls with  $P < 0.001$  (Figure 3).



**Figure 3: The tone of newborns studied.**

Among the 100 neonates in case group, 58 (58%) had no seizures. 42 (42%) had seizures as an abnormal neurological examination finding. Abnormal neurological examination is significantly more (42.0%) in cases when compared to Controls with  $P < 0.001$  (Figure 4).

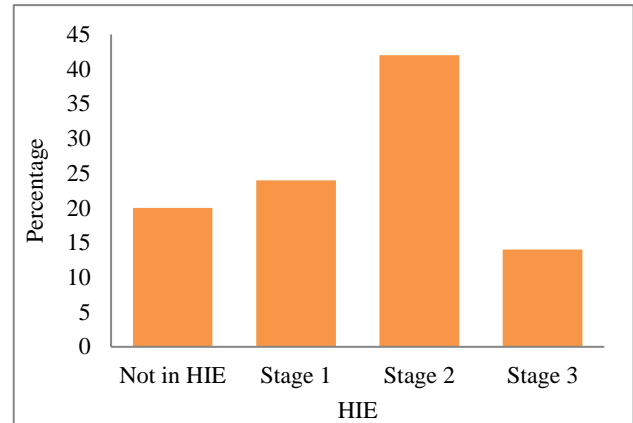


**Figure 4: Showing the number of neonates studied havin seizures.**

Among the 100 neonates in the case group, 20 (20%) were not in HIE, 24 (24%) had mild HIE, 42 (42%) had moderate HIE and 14 (14%) had severe HIE during the course in NICU (Figure 5). Out of 100 neonates enrolled in the case group having suffered asphyxia 94 (94%) were discharged, 6 (6%) died.

UUA/Cr ratio is significantly higher in study group compared to Control with  $t = 11.052$ ;  $P < 0.001$  (Table 3).

The study proved positive correlation between the urinary UA/Cr ratio and the severity (grading) of HIE ( $P < 0.001$ ) (Table 4).



**Figure 5: HIE staging of asphyxiated newborns.**

**Table 3: Comparison of urinary UA/CR ratio in the two groups studied.**

Urinary UA/CR	Cases	Controls
Min- max	0.78 – 4.94	0.42 – 1.96
Mean ±SD	2.58±1.09	0.86±0.17
Inference	Urinary UA/CR ratio is significantly higher in study group when compared with control group with $t = 11.052$ ; $P < 0.001^{**}$	

**DISCUSSION**

The results of the present study were in concordance with those of Reem Mahmoud and Dina El Abd (2010) who reported Urinary UA/Cr ratios were higher in asphyxiated infants ( $2.9 \pm 0.73$ ) when compared with the controls ( $0.72 \pm 0.35$ ,  $P < 0.001$ ). UA/Cr ratios were significantly higher in infants with severe HIE ( $3.18 \pm 0.61$ ) when compared with infants with moderate HIE ( $2.19 \pm 0.32$ ;  $P < 0.01$ ) and those with mild HIE ( $1.53 \pm 0.25$ ;  $P < 0.001$ ). The values of the UA/Cr ratios in the mild and moderate HIE groups (group Ia vs Ib) were also statistically significant ( $P < 0.01$ ).<sup>9</sup>

The above study also found sex of the baby and birth weight of the neonate not to be statistically significant difference between the cases and control groups. But mode of delivery was found to be statistically significant in both studies with the cases group having statistically significant more number of instrumental deliveries as well as caesarean sections. Also, the APGAR score at 1 minute, 5-minute, 10 minutes to statistically significant between the case and the control group there by being helpful as an important tool for birth asphyxia diagnosis and its severity.

**Table 4: Correlation of the ratio of urinary uric acid and creatinine (UUA/CR) with HIE status in cases studied.**

Urinary UA/CR	Total number of cases (n = 100)	HIE stage				P value
		Not in HIE (n = 20)	Stage 1 (n = 24)	Stage 2 (n = 42)	Stage 3 (n = 14)	
Min-max	0.78 -4.94	0.78-2.65	1.62-3.48	2.18-3.92	3.72-4.94	
Mean ± SD						

Also in a study conducted by Pallab Basu et al, it was found that urinary UA/Cr ratio was significantly higher in cases than controls ( $p < 0.001$ ) which is similar to our study.<sup>10</sup> It was also found that there was significant difference between Apgar scores of cases than controls ( $p = 0.02$ ).

There were also significant differences of mean urinary UA/Cr ratio for Apgar score 4-6 vs Apgar score 0-3 ( $p < 0.001$ ) which is also similar to our study where apgar at 1min, 5min and 10min were found to be useful in diagnosis of asphyxia and its severity. The study by Lofty M. El-Sayed et al also reported that urinary uric acid to creatinine ratio in term and preterm infants was significantly higher in the asphyxia group than in non-asphyxiated group.

He also proved simultaneously that this ratio was 76.6% sensitive, 83% specific, 80% accurate; with positive predictive value of 82.1% and negative predictive value of 78.1% hence concluding that this test allows rapid recognition of neonatal asphyxia, its severity assessment and potential to predict the short-term morbidity or death as well as the long-term outcome.<sup>11</sup>

Dong Wen Bin et al, in his study displayed that neonates who had been suffered from asphyxia have higher level of urinary uric acid to creatinine ratio as compared to the non-asphyxiated neonates. It may be used as an indicator for early assessment of apyxiyal severity and also renal injury in post asphyxia neonates.<sup>12</sup>

## CONCLUSION

The ratio of UA/Cr enables early and rapid recognition of asphyxial injury and also the assessment of its severity and the potential for short term morbidity or death. Although a variety of indicators for birth asphyxia are there, not even a single indicator has been found to be predictive of subsequent morbidity. Historically the Apgar scores had been used to define asphyxia and attempt outcome prognostication.<sup>13</sup>

However, we found the UA/Cr ratio to be a good, simple screening test for the early assessment of perinatal asphyxia, Furthermore, there is a correlation between the UA/Cr ratio and the severity of the encephalopathy, indicating the degree of injury at an early stage when

other quantitative methods frequently cannot be carried out.

However, this ratio does not provide further prognostic information that must be obtained by other methods.

*Funding: No funding sources*

*Conflict of interest: None declared*

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

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**Cite this article as:** 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;5:5418-23.