Original Research Article

Study of urinary uric acid to creatinine ratio as a biochemical marker of perinatal asphyxia and its correlation with Apgar Score

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ABSTRACT

Background: Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Every hour, 104 children die as a result of asphyxia. In India; between 250,000 to 350,000 infants die each year secondary to birth asphyxia and mostly within the first three days of life. The present study was performed to determine the Urinary Uric Acid to Creatinine Ratio in perinatal asphyxia and its correlation between APGAR score and urinary uric acid to creatinine ratio in perinatal asphyxia.

Methods: A randomized case control hospital-based study was conducted on 50 asphyxiated and 50 normal newborn. Urinary uric acid and creatinine were estimated in spot urine within 24 hours after birth in both cases and controls. A ratio between the concentrations of uric acid to creatinine was estimated and comparison done between cases and controls.

Results: Urinary uric acid to creatinine ratio can be used as an additional non-invasive, easy and early biochemical marker of birth asphyxia which biochemically supports the clinical diagnosis and the severity grading of asphyxia by APGAR score.

Conclusions: Urinary uric acid to creatinine ratio can be used as an additional non-invasive, easy and early biochemical marker of birth asphyxia which biochemically supports the clinical diagnosis and the severity grading of asphyxia by APGAR score.

Keywords: APGAR score, Perinatal asphyxia, Urinary uric acid/creatinine ratio

INTRODUCTION

Perinatal asphyxia is a condition in which there is an impaired gas exchange leading to hypoxemia, hypercapnea, and acidosis in fetus or neonate. Perinatal hypoxia is one of the leading causes of perinatal mortality in the developing countries. Globally hypoxia of the newborn (birth asphyxia) or the fetus (stillbirth) is estimated to account for 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year.[1] Data from National Neonatal Perinatal database (NNPD) suggests that, perinatal asphyxia is contributing to almost 20% of neonatal deaths in India.[2] In addition to this, ante-partum and intra-partum asphyxia contributes to 300,000 to 400,000 stillbirths.[2] In India, 8.4% of inborn babies have 1 minute APGAR score less than 7 and 1.4% suffers hypoxic ischemic encephalopathy (HIE).[2] Birth asphyxia is an important cause of static developmental and neurological handicap in both the term and preterm neonates (in 3 to 13% of infants with cerebral palsy (CP) have evidence of Intrapartum asphyxia).[3] Though there are many studies and understanding of the mechanisms leading to birth asphyxia, early determination of the tissue damages due to birth asphyxia are still lacking. APGAR score is most commonly used as diagnostic and prognostic indicator of birth asphyxia, the 1-minute APGAR score reflects the need for immediate resuscitation. The change in score between 1 and 5

minutes is a useful index for the effectiveness of resuscitative efforts. APGAR score alone does not predict neurological outcome since it is influenced by various factors such as immaturity, fetal malformations, maternal medications and infection. Accurate assessment of late neurological damage has failed by implementing strategies such as fetal heart monitoring,[4]apgar score,[5] while analysis of xanthine, hypoxanthine, neuron-specific enolase, brain-specific creatine kinase and inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1-beta, interleukin-8, interleukin-6) are time consuming, costly and not routinely available for clinical care.[4-9]

Brief hypoxia impairs cerebral oxidative metabolism leading to an anaerobic glycolysis to generate ATP. During anaerobic glycolysis, one molecule of glucose yields only 2 molecules of ATP as opposed to yielding 38 molecules of ATP during aerobic conditions. During prolonged hypoxia, cardiac output falls and cerebral blood flow is compromised. A combined hypoxic-ischemic insult produces failure of oxidative phosphorylation and ATP production, sufficient to cause the cellular damage. Lack of ATP and increase excitotoxin will leads to cellular damage and accumulation of adenosine diphosphate and adenosine monophosphate, which is later catabolized to adenosine, inosine and hypoxanthine. If there is uninterrupted tissue hypoxia and reperfusion injury, hypoxanthine is oxidized to xanthine and uric acid in the presence of xanthine oxidase leading to an increase in uric acid production, which come out in blood from tissues and excreted in urine.

METHODS

The study was conducted in the neonatology unit of Department of Pediatrics, between January 2016 and June 2017. The Ethical Committee of the medical faculty approved it, and written informed consent was taken from parents.

The study included 50 asphyxiated new-borns as a cases group and 50 healthy new-borns a control group. For cases.

Inclusion criteria

- Gestational age ≥ 37 weeks.
- Appropriate for gestational age.
- Intrapartum signs of fetal distress.
- APGAR score of < 7 min at one minute of life.
- Resuscitation with >1 min of positive pressure ventilation before stable spontaneous respiration.
- Mild, moderate or severe hypoxic ischemic encephalopathy as defined by Sarnat and Sarnat.

Exclusion criteria

- Congenital malformations.
- Maternal drug addiction.

- Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opioids (pharmacological depression).
- Hemolytic disease of new-born.
- Neonates born to mothers consuming alcohol.
- Neonates born to mothers who are smokers.
- New-borns born to mothers on antiepileptics.

The control group includes 50 healthy term new-borns, appropriate for gestational age without signs of perinatal asphyxia as evidenced by normal fetal heart patterns, clear liquor and 1 min Apgar score ≥ 7.

Method of data collection

Detailed maternal history, birth events, Apgar score, sex of the baby and weight of the baby were recorded. Gestational age was assessed by new Ballard scoring system. Thorough clinical and Neurological examination was done for all the neonates included in the cases group.

The spot urine samples were collected within 6-24 h of life and analyzed in the hospital laboratory immediately. Urinary uric acid was estimated in auto-analyzer (Roch / Hitachi 917auto analyzer) by enzymatic colorimetric assay uricase method.[10] Urinary creatinine was estimated in the same above instrument by using modified kinetic Jaffe's method.[10]

Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. Spearman's correlation was done to find the correlation between two quantitative variables and qualitative variables respectively.

The patients were also classified in three groups on the basis of their APGAR scores at 1min, 5min, and 10 min. The results of the patients were compared with their APGAR scores to determine the utility of the ratio in determining the severity of asphyxia.

RESULTS

Present study revealed significant increase in Uric acid/Creatinine ratio in early spot urine samples from asphyxiated newborns compared to non-asphyxiated (P value < 0.001).

Present study also proved that there is negative linear correlation between urine Uric acid/Creatinine ratio and

APGAR score at 1 min, 5 min and 10 min among asphyxiated newborn (p valve < 0.001).

Present study also proved that there is significant difference in APGAR score at 1min, 5min and 10 min in cases compared to control group (p valve < 0.001). Table 1 represents that 50 cases and 50 controls were included in the study. Mean gestational age of cases was 37.2 weeks whereas mean gestational age of controls was 37.3 weeks. Mean birth weight of cases was 2.6±0.4 kg and control were 2.8±0.4 kg.

Table 1: The demographic profiles of cases and controls.

Parameter	Cases	Control
Total number	50	50
Gestational age	37.2	37.3
Mean birth weight	2.6±0.4	2.8±0.4
Male/female	30/20	30/20
Number of vaginal delivery	27	42
Number of LSCS	23	8

Among 50 cases, 60% were males and 40% were females whereas among 50 controls, 60% were males and 40% were females. Mean birth weight was slightly lower among new-borns with asphyxia as compared to new-borns without asphyxia (2.92±0.67 kg vs. 3.06±0.71 kg).

Among cases, 44% were born through vaginal delivery while 54% were born through caesarean section, whereas among controls 84% were born through vaginal delivery while 16% were born through caesarean section. Table 2 signifies that urinary UA/CR ratio was significantly higher in cases than controls (2.8±0.9 vs 0.8±0.2; p< 0.001).

Table 2: Comparison of urinary uric acid/creatinine ratio in cases and control group.

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
UUA/CR	2.8	0.9	0.8	0.2	<0.001*

Table 3 hightlights that there was significant difference between Apgar scores of cases than controls.

Table 3: Apgar score at 1 min, 5 min and 10 min comparison between cases and controls.

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
1 Min	2.9	1.1	7.6	0.7	<0.001*
5 Min	5.1	1.0	8.6	0.6	<0.001*
10 Min	7.1	0.8	9.9	0.3	<0.001*

In the study at 1 min mean APGAR score among cases was 2.9±1.1 and among controls was 7.6±0.7. This difference in APGAR score between cases and controls was statistically significant. Similarly, at 5 min mean APGAR score among cases was 5.1±1.0 and among controls was 8.6 ± 0.6. This difference in APGAR score between cases and controls was statistically significant. Similarly, at 10 min mean APGAR score among cases was 7.1±0.8 and among controls was 9.9±0.3. This difference in APGAR score between cases and controls was statistically significant. Table 4 represents Spearman's negative correlation between UUA/CR ratio and APGAR score at 1 min, 5 min and 10 min among cases and it is statistically significant (p valve < 0.001).

Table 4: Spearman's correlation between Urinary UA/CR ratio and APGAR score at 1 min, 5 min and 10 min among cases.

			UUA/CR	1 Min	5 Min	10 Min
Spearman's rho	UUA/CR	Correlation Coefficient	1.000	-0.638**	-0.620**	-0.612**
		P value		<0.001*	<0.001*	<0.001*
		N	30	30	30	30

Table 5: Spearman's correlation between Urinary UA/CR ratio and APGAR score at 1 min, 5 min and 10 min among control.

			UUA/CR	1 Min	5 Min	10 Min
Spearman's rho	UUA/CR	Correlation Coefficient	1.000	-0.091	-0.124	0.040
		P value		0.632	0.514	0.835
		N		30	30	30

Table 5 highlights Spearman's correlation between UUA/CR ratio and APGAR score at 1 min, 5 min and 10 min among control and it is statistically not significant.
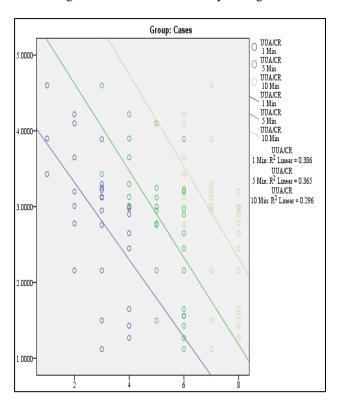

Figure 1: Scatter Plot showing Negative linear correlation between UUA/CR and APGAR score at 1 min, 5 min and 10 min among cases.
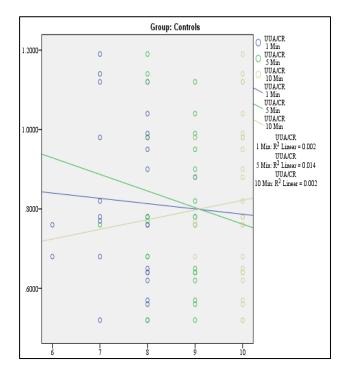

Figure no 2: Scatter Plot showing correlation between UUA/CR and APGAR score at 1 min, 5 min and 10 min among control.

DISCUSSION

Perinatal asphyxia is common cause of neonatal morbidity and mortality in developing country. There are various methods available to diagnose perinatal asphyxia such as magnetic resonance tomography, cranial tomography, and somatosensory evoked potentials. But these modalities are not useful in first 24 hours of life after birth. pH, lactates and base deficits can also use to diagnose birth asphyxia. Usually, 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. The APGAR score has a limited role in predicting the immediate outcome, such as that of HIE and the long-term sequelae.

In present study Urinary uric acid and creatinine ratios were significantly higher in cases (asphyxiated) than controls (normal newborn), (mean UUA/CR ratio in Cases was 2.8 ± 0.9 and in controls was 0.8 ± 0.2; P < 0.001) and among asphyxia patients, a significant negative linear correlation was found between the urinary uric acid to creatinine ratio and the APGAR score (r = -0.638 at 1 min, r = -0.620 at 5 min, r = -0.612 at 10 min, P < 0.001).

In study by Basu et al. found that urinary UA/CR ratio was significantly higher in cases than controls (3.1 ± 1.3 vs. 0.96 ± 0.54; p<0.001). Results are similar to present study.[11]

In study by Bader et al. found that urinary UA/CR ratio was higher in the asphyxiated group compared to controls. ($2.06+1.12$, vs. $0.64+0.48$; P<0.001). Results correlate with present study.[12]

In study by Chen et al. found that urinary UA/CR ratio was higher in the asphyxiated group compared to controls. This result supports present study.[13]

Present study also supported by study done by Kumar et al. which show that urinary UA/CR ratio was higher in the asphyxiated group compared to controls.[14]

In study by Bahubali et al. found that urinary UA/CR ratio was higher in the asphyxiated group compared to controls, they also reported a significant negative correlation between this ratio and the APGAR score.[15] Similar results are given by studies done by Banupriya, Bhongir and Nariman S.[16,17,18] In present study also, we found a significant negative linear correlation between urinary UA/CR ratio and the APGAR score.

CONCLUSION

It is imperative to do early diagnosis of perinatal asphyxia, since early start of therapy can prevent further complication associated with perinatal asphyxia. Various tests are available such as magnetic resonance

tomography, cranial tomography, and somatosensory evoked potentials. But these modalities are not useful in first 24 hrs of life after birth. pH, lactates and base deficits can also use to diagnose birth asphyxia. Usually, 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.

So, we conclude that urinary uric acid/ creatinine ratio is significantly high in babies with birth asphyxia and there is significant negative linear correlation between urinary uric acid/ creatinine ratio and Apgar score at 1 min, 5 min and 10 min among asphyxiated babies. This study was done in single centre with small sample size, so results cannot be generalised, needs further studies with large sample size. Many of birth asphyxia babies do not pass urine in first 24 hrs of life.

In present study, we did not correlate urinary uric acid/ creatinine ratio with other biochemical markers.

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