CORRELATION BETWEEN APGAR SCORE AND URINARY URIC ACID TO CREATININE RATIO IN PERINATAL ASPHYXIA

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ABSTRACT

A randomized case control hospital based study was conducted over 12 months time on 31 asphyxiated and 31 normal newborn to see whether urinary uric acid can be used as a marker of perinatal asphyxia and can be correlated with the clinical diagnosis by Apgar score. Uric acid and creatinine were estimated in spot urine within 24 hours after birth in both cases and controls. A ratio between concentrations of uric acid to creatinine was estimated and compared between cases and controls. It was found that the ratios were significantly higher in cases than controls (3.1 ± 1.3 vs 0.96 ± 0.54 ; $P < 0.001$) and among asphyxia patients, a significant negative linear correlation was found between the uric acid to creatinine ratio and the Apgar score ($r = -0.857$, $P < 0.001$). So urinary uric acid to creatinine ratio can be used as an additional non-invasive dispace, easy and at the same time early biochemical marker of birth asphyxia which biochemically supports the clinical diagnosis and severity grading of asphyxia by Apgar score.

KEY WORDS

Perinatal Asphyxia, Apgar score, Urinary uric acid to creatinine ratio.

INTRODUCTION

Perinatal hypoxia is one of the leading causes of perinatal mortality in developing countries. Birth asphyxia is an important cause of static developmental and neurological handicap both in term and preterm infants (in 3 to 13% of infants with cerebral palsy (CP) have evidence of intrapartum asphyxia) (1). Though there are more and more studies and understanding of the mechanisms leading to birth asphyxia, early determination of tissue damages due to birth asphyxia are still lacking.

Brief hypoxia impairs cerebral oxidative metabolism leading to an anaerobic glycolysis to generate ATP. During anerobic conditions one molecule of glucose yields only 2 molecules of ATP as opposed to producing 38 molecules of ATP during aerobic conditions. 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. 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.

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 calculation (2, 3).

MATERIALS AND METHODS

The study was conducted in the neonatology unit of Department of Pediatrics, on 62 newborn babies delivered between February, 2007 and January, 2008. Out of them 31

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babies were asphyxiated and rest 31 were healthy newborn. Written informed consents were taken from the parents of the babies. Cases and controls were randomly selected applying inclusion-exclusion criteria irrespective of body weight and maturity of the babies.

The selection criteria included newborn babies, admitted to the Neonatal Intensive Care Unit (NICU) with an Apgar score of 6 or less at 5 minutes of birth. Babies with congenital malformations, suspected metabolic disease on treatment with diuretics, suffering from anuria and those born to mothers having hypertension, diabetes mellitus, toxemia of pregnancy, receiving general anesthesia, Pethidine, phenobarbitone and other drugs likely to cause depression in babies and mother with history of febrile attack within 2 weeks before delivery were excluded from the study. Newborn in the control group were born after an uncomplicated pregnancy and had Apgar scores ≥ 7 at 5 minutes and no signs of asphyxia.

The urine samples were collected in the first 24 hours of delivery and analyzed in the hospital laboratory immediately. Spot single urine samples were considered. Urinary uric acid was estimated in auto-analyzer (model ERBA XL 600) by spectrophotometric uricase method (4). Urinary creatinine was estimated in the same above instrument by using modified kinetic Jaffe's method (5).

The results of the cases and controls were compared. Statistical comparison of measured values between the two groups were performed by the two tailed unpaired t test of the means. Bivariate distribution analysis was used to determine the correlations {two-tailed Karl Pearson's coefficient of correlation (indicated as "r") was used to identify the correlation between numerical variables}. Confidence intervals at 95% confidence limit of the parameters were also determined.

The patients were also classified in two groups on the basis of there Apgar scores. Babies with moderate asphyxia (Apgar score between 6 and 4) (6) were kept in one group and those with severe asphyxia (Apgar score between 3 and 0) (6) were in other group. The results of the patients were compared with their Apgar scores in order to determine the utility of the ratio in determining the severity. The statistical data analysis was done using SPSS software.

RESULTS

The demographic profiles of cases and controls are shown in Table 1.

Table 1: Demographic profile

	Cases	Controls
Total number	31	31
Mean body weight	2.42 $\pm$ 0.44 kg	2.56 $\pm$ 0.52 kg
Female / male	16 / 15	12 / 19
No. of vaginal delivery	12	26
No. of elective cesarean section	—	5
No. of emergency cesarean section	19	—

It was found that urinary UA/Cr ratio was significantly higher in cases than controls (3.1 ± 1.3 vs 0.96 ± 0.54 ; $p < 0.001$). It was also found that there was significant difference between Apgar scores of cases than controls (3.8 ± 1.4 vs 9.60 ± 0.38 ; $p = 0.02$). A significant negative linear correlation was found between urinary UA/Cr ratio and the Apgar score ($r = -0.857$, $p < 0.001$) among cases. No significant correlation was found between urinary UA/Cr ratio and the Apgar score among controls ($r = -0.298$, $p < 0.103$). Mean urinary UA/Cr ratio for Apgar score 4 – 6 were 1.97 ± 0.32 vs 0.96 ± 0.54 ; $p < 0.003$ (cases vs. controls) and Apgar score 0 – 3 were 4.24 ± 0.81 vs 0.96 ± 0.54 ; $p < 0.001$ (cases vs. controls). There were also significant differences of mean urinary UA/Cr ratio for Apgar score 4 – 6 vs Apgar score 0 – 3 ($p < 0.001$). Confidence intervals are shown in Table 2. Correlation between urinary UA/Cr ratio and Apgar score in cases is illustrated in Figure 1.

**Figure 1 : Linear regression analysis
Correlation between Apgar score & UA/Cr**

DISCUSSION

This study shows that uric acid in a single urine sample was elevated in neonates with birth asphyxia as compared to the control. In addition, UA/Cr ratios in the early urine samples within 24 hours of birth of these asphyxiated infants were correlated significantly with the clinical severity of the disease.

Low Apgar score is the most accepted diagnostic as well as prognostic indicator of asphyxia in neonate till date. But Apgar score may be depressed in conditions like babies with congenital anomalies or preterm premature newborns. So the clinical diagnosis of asphyxia by Apgar scores must be supported by some investigations which are easy and at the same time early so that early decision can be taken about the level of care the baby needs. Usually pH, lactates and base deficits subsides with the establishment of respiration, and with other mode of resuscitation. However pH, lactate, base deficit estimations are invasive and require sophisticated instruments also. To solve these problems non-invasive urinary UA/Cr ratio may be an answer.

Purine degradation products such as hypoxanthine, xanthine and uric acid are useful clinical indicator of tissue hypoxia (7, 8). During the hypoxia and reoxygenation period after asphyxia, accumulated hypoxanthine is oxidized to uric acid, and a high level of these substances being released from tissues into the circulation is ultimately excreted through urine. Detection of hypoxanthine and xanthine requires sophisticated techniques (like, High Performance Liquid Chromatography or HPLC) (9) and instruments which are impractical in maximum neonatal setup. But for urinary uric acid and creatinine estimations, only very simple instruments like photoelectric colorimeter or semi-auto-analyzer, simple reagents and simple techniques are required and can be acquired at low costs. Uric acid through urine passes out in four steps: glomerular filtration, tubular reabsorption, active secretion and post secretory reabsorption. Infants with birth asphyxia had renal function within normal limit as reflected by similar creatinine concentrations in spot urine both in cases and control group. High values of uric acid, corrected for creatinine to control for urine volume, may therefore suggest more uric acid generation among asphyxia cases. Urinary UA/Cr ratio in this study finds some similarity with the studies undergone by Bader et al and Erdag et al. Bader et al (10)

showed that these ratios had significant correlation with the asphyxia score, and the mean UA/Cr ratio was in normal babies less than 1. Erdag et al (11) also demonstrated in their study that in control group the mean ratio is within 1 where as those with asphyxia present definite higher ratio with mean value as 2.29. In the current study mean UA/Cr ratio is 3.1 in cases against 0.96 in control group and 95% of the mean lie between 2.68 – 3.59 (cases) vs 0.76 – 1.15 (controls). Chen et al (12) concluded that mean UA/Cr ratio among healthy premature control group was higher than that of healthy control group. In the current study, cases and controls were selected irrespective of the body weight and maturity. So further separate study is required among premature babies to review their studies.

The ratio can be used as early, cost effective, simple, quick and non-invasive parameter, a supportive tool to the diagnosis of birth asphyxia using Apgar score and in determining its severity by simple biochemical test. Finally it concludes that Apgar score is still a significant tool in diagnosis and severity calculation of birth asphyxia. So where we have simplest health care setup with minimum diagnostic backup, combined application of Apgar score and urinary UA/Cr ratio can help early and definite interventions and in early decision making about the level of care the baby requires.

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Table 2: Confidence intervals at 95% confidence level of different parameters in cases and controls

Parameters	Confidence intervals at 95% confidence level of parameters*	
	Lower limit	Upper limit
Urinary UA/Cr ratio in cases	2.68	3.59
Urinary UA/Cr ratio in controls	0.76	1.15
Apgar score among cases	2.43	5.24
Apgar score among controls	9.50	9.77

*95% chance that the population means lie in the range between lower and upper limits.

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