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Clinical evaluation of levels of urinary uric acid and creatinine ratio in neonatal asphyxia cases

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Abstract
Perinatal asphyxia contributes significantly to neonatal morbidity and mortality. Factors like poverty, ignorance and lack of medical facilities and obstetric care (only a third of deliveries being institutional) contribute significantly to the magnitude of the problem of perinatal asphyxia in our country although a common condition, there is generally no accepted definition for birth asphyxia. It is a devastating clinical condition because of its potential for causing permanent damage, even death of the fetus or newborn baby. 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 The present study was planned to evaluate the urinary uric acid to creatinine ratio in perinatal asphyxia and showing increased uric acid and creatinine excretion in early spot urine for identification of perinatal asphyxia and to assess the severity of hypoxic ischaemic encephalopathy as a marker of severity of perinatal asphyxia in term babies and its correlation to APGAR score.
The present study was planned in Department of Pediatrics, Government Medical College Bettiah, West Champaran, Bihar. Total 25 cases of the neonatal asphyxia were evaluated in the present study. For comparative evaluation 25 normal cases of the neonates were enrolled in the control group patients. 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.
The data generated from the present study concludes that urinary UA/Cr ratio increases considerably after birth asphyxia, and the increase is associated with severity of HIE with a poorer outcome. Hence, UA/Cr ratio might have an important role in diagnosing and predicting the outcome of perinatal asphyxia although there is a need for a large population based prospective study including preterm and term newborns to determine cut off values of urinary UA/Cr ratio for the severity of perinatal asphyxia.

Keywords: creatinine, HIE, perinatal asphyxia, Uric acid, etc

1. Introduction
Perinatal asphyxia (also known as neonatal asphyxia or birth asphyxia) is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. It is also the inability to establish and sustain adequate or spontaneous respiration upon delivery of the newborn. It remains a serious condition which causes significant mortality and morbidity. It is an emergency condition and requires adequate and quick resuscitation measures. Perinatal asphyxia is also an oxygen deficit from the 28th week of gestation to the 1st 7days following delivery. It is also an insult to the fetus or newborn due to:lack of oxygen, lack of perfusion to various organs and may be associated with lack of ventilation.
In accordance with WHO, perinatal asphyxia is characterised by- Profound metabolic acidosis, with a PH <7.20 on umbilical cord arterial blood sample, Persistence of an APGAR score of 3 at the 5th minute, Clinical neurologic sequelae in the immediate neonatal period, Evidence of multiorgan system dysfunction in the immediate neonatal period. Hypoxic damage can occur to most of the infant's organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal. In more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity.
It results most commonly from antepartum causes like a drop in maternal blood pressure or some other substantial interference with blood flow to the infant's brain during delivery. This can occur due to inadequate circulation or perfusion, impaired respiratory effort, or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term, and more for those that are born prematurely [1]. WHO estimates that 4 million neonatal deaths occur yearly due to birth asphyxia, representing 38% of deaths of children under 5 years of age [2].
Perinatal asphyxia can be the cause of hypoxic ischemic encephalopathy or intraventricular hemorrhage, especially in preterm births. An infant suffering severe perinatal asphyxia usually has poor color (cyanosis), perfusion, responsiveness, muscle tone, and respiratory effort, as reflected in a low 5 minute Apgar score. Extreme degrees of asphyxia can cause cardiac arrest and death. If resuscitation is successful, the infant is usually transferred to a neonatal intensive care unit.
There has long been a scientific debate over whether

newborn infants with asphyxia should be resuscitated with 100% oxygen or normal air [3]. It has been demonstrated that high concentrations of oxygen lead to generation of oxygen free radicals, which have a role in reperfusion injury after asphyxia [4]. Research by Ola Didrik Saugstad and others led to new international guidelines on newborn resuscitation in 2010, recommending the use of normal air instead of 100% oxygen [5, 6]. There is considerable controversy over the diagnosis of birth asphyxia due to medicolegal reasons. Because of its lack of precision, the term is eschewed in modern obstetrics. Asphyxia is a common occurrence during the neonatal period. Although it is a major contributor to neonatal morbidity and mortality, the diagnosis and evaluation of asphyxia can be problematic.

Neonatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Globally, hypoxia of the newborn (birth asphyxia) or the fetus ("fresh stillbirth") is estimated to account for 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year [7]. An estimated 1 million children who survive birth asphyxia live with chronic neurodevelopmental mfvorbidities, including cerebral palsy, mental retardation, and learning disabilities. In India, between 250,000 to 350,000 infants die each year due to birth asphyxia, mostly within the first three days of life. In addition, ante-partum and intra-partum asphyxia contributes to as many as 300,000 to 400,000 stillbirths. In India, 8.4% of inborn babies have a one minute Apgar score less than 7 and 1.4% suffer from hypoxic ischemic encephalopathy (HIE) [8]. Accurate estimates of the proportion of neonatal mortality attributable to birth asphyxia are limited by the lack of a consistent definition for use in community-based settings and the absence of vital registration in communities where the majority of neonatal deaths occur.

Only a third of deliveries in India are institutional and many asphyxiated babies are brought late to hospitals. The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose neonatal asphyxia.

Although asphyxia is associated with multiple organ injuries, especially with adverse neurological outcomes, management still focuses on supportive care. So, if the adverse effects of hypoxia on the newborn are considered, there is a need to identify infants who will be at high risk for hypoxic ischemic encephalopathy and early neonatal death as a consequence of neonatal hypoxia. A variety of markers have been examined to identify neonatal hypoxia including electronic fetal heart monitoring, low Apgar scores, cord pH, electroencephalograms, computed tomography (CT) and magnetic resonance imaging (MRI) scans and Doppler flow studies. Supplementary methods for diagnosis and prediction of antenatal and non-acidotic prolonged asphyxia are lacking.

Neonatal asphyxia may result in adverse effects on all major body systems. Many of these complications are potentially fatal. In a term infant with perinatal asphyxia renal, neurologic, cardiac and lung dysfunction occurs in 50%, 28%, 25% and 23% cases respectively. The extent of multi-organ dysfunction determines the early outcome of an asphyxiated neonate with either the neonate succumbing as a consequence of organ damage or recovering completely. Generally there are no long term sequelae associated with these organ system derangements. Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with perinatal asphyxia. HIE is foremost concern in an asphyxiated neonate because contrary to other system derangements this has the potential to cause serious long term neuromotor sequelae among survivors. The neuro-developmental delay cannot be assessed with currently used diagnostic methods in the patients with perinatal asphyxia or Hypoxic-Ischemic Encephalopathy(HIE)) [9].

Neonatal asphyxia causes neurological morbidity and mortality in full-term infants. Despite the increasing understanding of the mechanisms leading to and resulting from neonatal asphyxia, early determination of brain damage following hypoxic-ischemic events still remains one of the hardest problems in neonatal care [10].

Neonatal hypoxia is one of the leading causes of neonatal 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). 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 ofATP 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. In the reoxygenation period, radicals are produced parallel to uric acid formation, which may be linked to the severity of perinatal asphyxia [11]. Urinary uric acid and creatnine in 24 hours urine sample is 250-750 mg/lit/24hrs and 1 to 2 gms/lit/24hrs respectively [12].

Uric acid level in spot urine of normal preterm AGA (appropriate for gestational age) babies in day one of their life. was 36.50 +/- 5.99 mg/dl in normal preterm neonates as compared to 18.40 +/- 0.45 mg/dl in normal term babies. [12]

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 lackin.

This study is to evaluate the utility of urinary uric acid to creatinine ratio (UA/Cr ratio) within 24 hours of birth 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 [13].

Perinatal asphyxia contributes significantly to neonatal morbidity and mortality. Factors like poverty, ignorance and lack of medical facilities and obstetric care (only a third of deliveries being institutional) contribute significantly to the magnitude of the problem of perinatal asphyxia in our country although a common condition, there is generally no accepted definition for birth asphyxia. It is a devastating clinical condition because of its potential for causing permanent damage, even death of the fetus or newborn

baby. 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 The present study was planned to evaluate the urinary uric acid to creatinine ratio in perinatal asphyxia and showing increased uric acid and creatinine excretion in early spot urine for identification of perinatal asphyxia and to assess the severity of hypoxic ischaemic encephalopathy as a marker of severity of perinatal asphyxia in term babies and its correlation to apgar score.

Methodology

The present study was planned in Department of Pediatrics, Government Medical College Bettiah, West Champaran, Bihar. Total 25 cases of the neonatal asphyxia were evaluated in the present study. For comparative evaluation 25 normal cases of the neonates were enrolled in the control group patients. 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.

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.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Gestational age ≥37weeks, 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.

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 opiods (pharmacological depression), Maternal drug addiction, Haemolytic 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.

Results & Discussion

Perinatal asphyxia is a common neonatal condition contributing significantly to neonatal morbidity and mortality. It is a devastating condition because of its potential to cause permanent damage and even death of the neonate. The signs of asphyxia injuries are non specific and may overlap with other illnesses. Due to limitations, the Apgar scores alone cannot be used as an useful tool for the evaluation of asphyxia in neonates. Birth asphyxia is the most common and important cause of preventable cerebral injury occurring in the neonatal period, but although asphyxia at birth is a commonly made diagnosis, there is generally no accepted definition for it. The term is used to imply an abnormal process and one that, if untreated, may cause permanent injury. Asphyxia, at a pathophysiological level, is the simultaneous combination of both hypoxia and hypoperfusion, which impairs tissue gas exchange leading to tissue acidosis.

There is no unanimity or consensus regarding the definition of birth asphyxia and various workers have used different definitions making it difficult to ascertain the incidence of asphyxia. The World Health Organization has defined birth asphyxia as "failure to initiate and sustain breathing at birth" and based on Apgar score as an Apgar score of <7 at one minute of life. The National Neonatal Perinatal Database (NNPD) 2000 used a similar definition for perinatal asphyxia and defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 and severe asphyxia as no breathing or an Apgar score of 0-3 at one minute of life. The National Neonatology Forum of India has defined asphyxia as "gasping or ineffective breathing or lack of breathing at one minute of life".

Low APGAR score is commonly used as an indicator of asphyxia in neonates, but it may often be not available and may be low in premature infants [14]. Other investigations may be required to support the diagnosis of asphyxia for early intervention. Blood pH values get quickly normalized after the onset of respiration, due to the elimination of carbon dioxide and cannot be relied upon specially in patients who are transferred from other centres. Additionally, lactate and base deficit are closely interconnected.

Table 1

Group of	Cases	Control
Cases of	**Asphyxia**	**Normal**
No. of Cases	**25**	**25**
Gestational age	36 – 37 weeks	36 – 37 weeks
Mean birth weight	2.1 – 3.3 kg	2.3 – 3.5 kg
Sex: Male Females	 18 7	 16 9
Number of vaginal delivery	17	20
Number of LSCS	8	5

Table 2: Apgar score

Group of	Cases	Control
Cases of	Asphyxia	Normal
No. of Cases	25	25
Apgar score at 1min.		
0 - 3	20	0
4 - 6	5	0
≥7	0	25
Apgar score at 5min.		
0 - 3	4	0
4 - 6	8	0
≥7	13	25
Apgar score at 10min		
0 - 3	0	0
4 - 6	4	0
≥7	21	25

Table 2: Uric Acid (UA) & Creatinine Score (CA)

Group of	Cases	Control
Cases of	Asphyxia	Normal
Urinary UA/CR	0.85 – 4.59	0.32 – 2.18

The present study revealed a significant increase in UA/Cr ratio in early spot urine samples from asphyxiated full term newborns and the study proved positive correlation between the urinary UA/Cr ratio and the severity (grading) of HIE (P< 0.001). Our results are similar to studies conducted by Pallab Basu *et al*, [15] Bader *et al*, [16] Akisu *et al*, [17] Mehes *et al* [18] and Vandana Verma *et al*. [19]

The suggestion that asphyxia occurs when there is hypoxia together with accumulation of carbon dioxide and if prolonged this leads to an eventual state of respiratory and then metabolic acidosis ignores the fact that this may be an entirely normal sequence of physiological events. Severe fetal or cord blood acidosis is a marker of impaired tissue gas exchange, but there is no evidence that acidosis per se is a cause of further tissue damage [20].

The umbilical artery pH that defines asphyxia of a sufficient degree to cause brain injury is unknown. The incidence of seizures and neonatal mortality is increased in neonates with an umbilical artery pH <7.0 directly after birth. But even below this very low pH level, the specificity is low with normal outcome reported in as many as 80% of neonates with an umbilical artery pH <7.0 [21]. There is an interesting study showing a high predictive value of arteriovenous pCO2 difference for identification of HIE after asphyxia. A limitation of cord blood gas as a predictor is illustrated in the newborn monkey where total asphyxia causes severe acidosis together with a decrease in pO2 and hypercapnia, while pH and pCO2 may remain normal during partial asphyxia where the respiratory gas exchange to the fetus is insufficient for a longer time diminishes gradually. This partial "non-acidotic" asphyxia still causes low pO2 and is followed by white matter injury [22].

One minute Apgar score generally correlates with umbilical cord blood pH and is an index of intrapartum depression. It does not correlate with outcome. Babies with a score of 0 to 4 have been shown to have significantly lower pH, high Paco2, and lower buffer base than those with Apgar scores > 7 [23]. Apgar score beyond 1 minute is reflective of the neonate's changing condition and the adequacy of resuscitative efforts.

Heavy or thick meconium staining is considered to be a marker of more prolonged or severe asphyxial episodes. Meconium staining is seen in approximately 15% of all labours and is present during labour in 11% of full-term pregnancies where there is no evidence, other than the meconium, of asphyxia. A normal fetal heart rate trace in labour appears to be a good indicator that metabolic acidosis is not developing, but a severely abnormal trace with late decelerations in the fetal heart rate is associated with significant fetal acidosis in only about 50% of cases [20].

Ninety percent of asphyxial insults occur in the antepartum or intrapartum periods as a result of placental insufficiency resulting in an inability to provide oxygen and remove carbon dioxide and hydrogen ion from the fetus. The remaining 10% are post-partum usually secondary to pulmonary, cardiovascular or neurologic insufficiency. A significant asphyxial insult to the fetus is likely to compromise a number of different organ systems of which the brain, kidneys and myocardium are particularly vulnerable. The presence of transient compromise to more than one organ is therefore a feature of a global asphyxial insult. The defence mechanism when a fetus is exposed to hypoxic-ischemia is based on the ability to centralize cardiac output to prioritised organs such as the brain, heart and adrenals at the expense of, for the moment, less important organs such as the liver, lungs, skin and muscles. Multi-organ dysfunction is a natural consequence of this defence mechanism because of the cellular damage inflicted on the non-prioritised organs.

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 ofATP 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.

Study done by Pallab Basu, *et al* found that urinary uric acid/Creatinine ratio within 24 hours of birth was significantly higher in asphyxiated neonates than non asphyxiated neonates [24]. G. Ciler Erdag, MD; A. Vitrinel, MD showed that Mean uric acid/creatinine ratio within 24 hours of birth in the asphyxiated neonates was more than while the mean ratio for the non asphyxiated neonates.The difference between the two groups was statistically significant ($p < 0.05$) [25].

Hsing-Jin Chen *et al* reported that the urinary ratio of Uric acid to Creatinine may be used as an marker of perinatal asphyxia .In term and premature infants significantly higher urinary ratio of UA to Cr in the asphyxia group than in the non asphyxiated group. In premature infants, the UA/Cr ratio was also significantly higher in the asphyxiated group than in the non asphyxiated group [26].

Lotfy M. El-Sayed *et al* in his study showed that the urinary ratio of Uric acid to Creatinine ratio in term and premature infants significantly higher urinary ratio of Uric acid to Creatinine in the asphyxia group than in the non asphyxiated group. Urinary UA/Cr ratio found to be accurate by 80%, sensitive 76.6%, specific 83%, with a positive predictive value of 82.1% and negative predictive value of 78.1. Thus concluded that urinary UA/Cr ratio allow for rapid recognition of asphyxia and assessment of its severity and potential for short-term morbidity or death as well as the prediction of the long-term outcome [27] Akisü M *et al* reported that the urinary ratio of Uric acid to Creatinine

in term and premature infants were significantly higher in the asphyxia group than in the non asphyxiated groupand found that UA/Cr ratio was a good, simple screening test for the early assessment of perinatal asphyxia [28].

Study done by David Bader, *et al* showed that the urinary ratio of Uric acid to Creatinine may be used as an marker of perinatal asphyxia as in term and premature infants significantly higher urinary ratio of UA to Cr was noted in asphyxia group than in the non asphyxiated group. This may be used as an indicator of the severity of perinatal asphyxia [29]. C. Banupriya, Ratnakar, *et al* concluded that Urinary excretion rate of uric acid higher in asphyxiated neonates as compared to the non-asphyxiated ones and has potential to act as biochemical markers for severity evaluation and death prediction in neonatal asphyxia [30]. DONG Wen Bin, *et al*. displayed in his study that neonates who have suffered asphyxia have a higher urinary UA/Cr ratio as compared 2 the non asphyxiated ones. It might be used as an indicator for early assessment of the severity of asphyxia and postasphyxial renal injuries in neonates [31].

Limitations of our study are methodological in nature. More details on asphyxiated neonates such as duration of labor, duration of resuscitation, time to first breath, etc may throw more light on the utility and limitations of the lab tests. We are also limited by the fact that this is single center study with a relatively small sample size. Multicentric studies with more sample size will allow us to utilize more variables in multivariate analysis and further improve upon the predictive value of this marker.

Conclusion

The data generated from the present study concludes that urinary UA/Cr ratio increases considerably after birth asphyxia, and the increase is associated with severity of HIE with a poorer outcome. Hence, UA/Cr ratio might have an important role in diagnosing and predicting the outcome of perinatal asphyxia although there is a need for a large population based prospective study including preterm and term newborns to determine cut off values of urinary UA/Cr ratio for the severity of perinatal asphyxia.

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