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Study of changes in levels of uric acid & creatinine levels in the neonates suffered from neonatal asphyxia

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Abstract
Perinatal asphyxia is one of the major cause of neonatal mortality and morbidity. It is an important cause of static developmental and neurological handicap in terms. So early detection and treatment can significantly reduce morbidity and mortality. Based on above clinical findings the present study was planned for study of changes in levels of uric acid & creatinine levels in the neonates suffered from neonatal asphyxia.
The present study was planned in Department of Pediatrics, Government Medical College, Bettiah, West Champaran, Bihar. Total 100 cases were enrolled in the present study. Out of the total enrolled cases 50 cases of suffered from the neonatal asphyxia were studied under Group I and another 50 cases without any complication were studied under Group II as control cases. The spot urinary sample within 24 hours is to be collected and is analyzed in hospital laboratory. Urinary uric acid was estimated by auto analyzer by spectrophotometric uricase method. Urinary creatinine was estimated in same above instrument by using modified kinetic Jaffe's method.
The data generated from the present study concludes 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. The urinary Uric Acid/Creatinine ratio in combination with the APGAR score and other scoring tools can contribute to early decision making on the level of care that infants require.

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

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 first seven days following delivery. It is also an insult to the fetus or newborn due to lack of oxygen or lack of perfusion to various organs and may be associated with a 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 [7]. Because of its lack of precision, the term is eschewed in modern obstetrics.
Despite major advances in monitoring technology and knowledge of fetal and neonatal pathologies, hypoxic-

ischemic encephalopathy (HIE) remains a serious condition that causes significant mortality and long-term morbidity. HIE is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia (ie, hypoxia, acidosis). Most often, the exact timing and underlying cause remain unknown. The American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) published guidelines to assist in the diagnosis of severe hypoxic-ischemic encephalopathy[8, 9].

Despite the fact that uric acid was first identified approximately 2 centuries ago, certain pathophysiologic aspects of hyperuricemia are still not clearly understood. For years, hyperuricemia has been identified with or thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities [10-11].

Unlike allantoin, the more soluble end product of purine metabolism in lower animals, uric acid is a poorly soluble end product of purine metabolism in humans. Human beings have higher levels of uric acid, in part, because of a deficiency of the hepatic enzyme uricase, and a lower fractional excretion of uric acid. Approximately two thirds of total body urate is produced endogenously, while the remaining one third is accounted for by dietary purines.

Approximately 70% of the urate produced daily is excreted by the kidneys, while the rest is eliminated by the intestines. However, during renal failure, the intestinal contribution of urate excretion increases to compensate for the decreased elimination by the kidneys.

The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion. Theoretically, alterations in this balance may account for hyperuricemia, although clinically defective elimination accounts for most cases of hyperuricemia.

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL. Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule. The recent cloning of certain urate transporters will facilitate the understanding of specific mechanisms by which urate is handled in the kidney and small intestines.

A urate/anion exchanger (URAT1) has been identified in the brush-border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan [12]. A human organic anion transporter (hOAT1) has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs, [13] while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells [14]. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate.

Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum concentration results in a marked increase in urate excretion. Hyperuricemia may occur because of decreased excretion (underexcretors), increased production (overproducers), or a combination of these two mechanisms. Underexcretion accounts for most causes of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, postsecretory reabsorption. Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency. Decreased tubular secretion of urate occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion. Finally, enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.

Overproduction accounts for only a minority of patients presenting with hyperuricemia. The causes for hyperuricemia in overproducers may be either exogenous (diet rich in purines) or endogenous (increased purine nucleotide breakdown). A small percentage of overproducers have enzymatic defects that account for their hyperuricemia. These include a complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) as in Lesch-Nyhan syndrome, partial deficiency of HGPRT (Kelley-Seegmiller syndrome), and increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity. Accelerated purine degradation can result from rapid cell proliferation and turnover (blast crisis of leukemias) or from cell death (rhabdomyolysis, cytotoxic therapy). Glycogenoses types III, IV, and VII can result in hyperuricemia from excessive degradation of skeletal muscle ATP.

Combined mechanisms (underexcretion and overproduction) can also cause hyperuricemia. The most common cause under this group is alcohol consumption [15], which results in accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion. Enzymatic defects such as glycogenoses type I and aldolase-B deficiency are other causes of hyperuricemia that result from a combination of overproduction and underexcretion.

Urate crystals can engage an intracellular pattern recognition receptor, the macromolecular NALP3 (cryopyrin) inflammasome complex [16-17]. NALP3 inflammasome may result in interleukin 1 (IL-1) beta production, which, in turn, incites an inflammatory response. Inhibition of this pathway has been targeted as a treatment for hyperuricemia-induced crystal arthritis, with recent reports documenting the efficacy of the IL-1 inhibitors canakinumab and rilonacept for preventing gout flares during the initiation of allopurinol therapy [18].

Zinc and magnesium are important nutrients with anti-inflammatory properties. Chinese studies have linked low dietary levels to hyperuricemia in men. A study by Xie *et al* in 2697 men and 2471 women indicated that dietary zinc intake was inversely associated with hyperuricemia in middle-aged and older males, but not in females [19]. Wang *et al* reported that in 5168 subjects, dietary magnesium intake was inversely associated with hyperuricemia, independent of some major confounding factors, but only in males [20]. In recent studies new biochemical parameters are being evaluated for early diagnosis of asphyxia. Uric acid is the end product of purine metabolism in humans. [21] During reoxygenation and reperfusion after asphyxia and ischemia, hypoxanthine accumulated in both circulating blood and tissue is oxidized to uric acid [22]. Since urinary creatinine can be used as the reference substrate in a spot urine sample, an increased uric acid to creatinine ration may be an absolute indicator of severity of tissue hypoxia in patients with intact renal functions [23]. The ratio of urinary uric acid

to creatinine helps in rapidly recognizing asphyxia and assessing its severity. Though numerous indicators for asphyxia are available, no single indicator has been found to be effective in predicting subsequent morbidity. Although many bio chemical indicators such as hypoxanthine, lactate, neuron specific enolase, brain iso enzyme of creatinine phosphokinase are reported, they are most useful for the purpose of research and still remain unavailable in most clinical services [24].

Perinatal asphyxia is one of the major cause of neonatal mortality and morbidity. It is an important cause of staticdevelopmental and neurological handicap in terms. So early detection and treatment can significantly reduce morbidity and mortality.Based on above clinical findings the present study was planned forstudy of changes in levels of uric acid & creatinine levels in the neonates suffered from neonatal asphyxia.

Methodology

The present study was planned in Department of Pediatrics, Government Medical College, Bettiah, West Champaran, Bihar. Total 100 cases were enrolled in the present study. Out of the total enrolled cases 50 cases of suffered from the neonatal asphyxia were studied under Group I and another 50 cases without any complication were studied under Group II as control cases.The spot urinary sample within 24 hours is to be collected and is analyzed in hospital laboratory. Urinary uric acid was estimated by auto analyzer by spectro photometric uricase method. Urinary creatinine was estimated in same above instrument by using modified kinetic Jaffe's method.

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

Term Babies admitted to NICU with apgar score of 6 or less at 5 minutes of birth and controls were apgar score >/=7 at 5 min with no signs of asphyxia

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, toxemia of pregnancy, receiving general anaesthesia, pethidine, phenobarbitone, and other drugs likely to cause depression ,in babies and mother febrile attack within 2 months before delivery were excluded from study.

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. Various factors especially prematurity has an effect on it as a result of which it may not predict mortality and morbidity definitely. In the absence of perinatal records, it is difficult to diagnose neonatal asphyxia retrospectively. We cannot precisely distinguish the false positively diagnosed from the true positive asphyxiated neonates. The role of various biochemical markers for diagnosing asphyxia is inadequate and controversial [25]. Although several biochemical indicators such as lactate, hypoxanthine, brain isoenzyme of creatinine phosphokinase, neuron specific enolase, excitatory amino acids and erythropoietin are reported, they are mostly useful in research and not available in most clinical services [26].

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. Hypoxia and ischemia can cause damage to almost every tissue and organ of the body with common involvement of kidneys, brain, heart and lungs. An estimated 1 million children who survive after experiencing asphyxia at birth are at higher risk of long-term morbidity such as cerebral palsy, mental retardation and learning disabilities.

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 1: Demographic Details

Group of	Group A	Group B
Cases of	Asphyxiated Babies	Normal Babies
No. of Cases	50	50
Weight	2.145 – 2869 gm	2210 – 3176 gm
Males/Female	31/19	28/22
No. of Vaginal Delivery	21	35
No. of Caesarean Section	29	15

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

Group of	Group A Asphyxiated Babies	Group B Normal Babies
Uric Acid (UA) & Creatinine Score (CA)	1.02 – 4.57	0.32 – 2.18

Table 3: Apgar score

Group of	Cases	Control
Cases of	Asphyxia	Normal
No. of Cases	50	50
Apgar score at 1min.		
0 – 3	41	0
4 – 6	9	0

≥7	0	50
Apgar score at 5min.		
0 – 3	9	0
4 – 6	17	0
≥7	24	50
Apgar score at 10min		
0 – 3	0	0
4 – 6	10	0
≥7	40	50

Purine degradation products such as hypoxanthine, xanthine and uric acid are useful clinical indicator of tissue hypoxia. [27-28] 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) [29] 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* [30] 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* [31] 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* [32] concluded that mean UA/Cr ratio among healthy premature control group was higher than that of healthy control group

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 [33]. 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 [34]. Similar results are given by studies done by Banupriya, Bhongir and Nariman S [35-37]. In present study also, we found a significant negative linear correlation between urinary UA/CR ratio and the APGAR score.

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.

Conclusion

The data generated from the present study concludes 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. The urinary Uric Acid/Creatinine ratio in combination with the APGAR score and other scoring tools can contribute to early decision making on the level of care that infants require.

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