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Original Research

Correlation of Urinary Uric Acid, Creatinine Ratio with the severity of Hypoxic Ischemic Encephalopathy

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***ABSTRACT*:**
Introduction: Perinatal asphyxia is a major cause of neonatal death worldwide. Hypoxic ischemic encephalopathy affects the tissues and it can lead to brain damage. The present study was aimed (a) To estimate urinary uric acid and creatinine levels in spot urine sample. (b) To correlate the urinary uric acid, creatinine ratio with severity of hypoxic ischemic encephalopathy. **Materials & methods:** This prospective study was conducted at Department of Paediatrics in RL Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Karnataka. A total of 108 term babies with ≥37 weeks of gestations with hypoxic ischemic encephalopathy were included. The babies who have suffered asphyxia and as per standard staging system (SARNAT AND SARNAT) which fit in to the criteria of Hypoxic Ischemic Encephalopathy be categorized in to stage 1, stage 2 and stage 3 were included in this study. The random urine samples were collected and analyzed for urinary uric acid and creatinine. P< 0.05 was considered significant. **Results:** In the present study, out of 108 neonates, 36 subjects had HIE 1, 40 had HIE 2 and 32 had HIE 3. Among the HIE 1 subjects, the median urine uric acid was 34 (17.25, 75.75), HIE 2 was 38.20 (20.75, 57.50) and HIE 3 was 35.50 (28, 60.45). Among the HIE 1 subjects, the median urine creatinine was 23.25 (14, 45.75), HIE 2 was 16.90 (10, 31.25) and HIE 3 was 10 (7.55, 15.05). The difference in the urine creatinine across HIE was statistically significant (P Value <0.001). Among the HIE 1, the median ratio was 1.26 (1.06, 2.20),HIE 2 was 2.07 (1.87, 2.50) and HIE 3 was 3.47 (2.85, 4.57). The difference in the ratio across HIE was statistically significant (P Value <0.001).A positive correlation was noted between severity of HIE and urinary uric acid creatinine ratio with r =0.6 and statistically significant value p =0.001 noted. **Conclusion:** Urinary UA/Cr ratio is an accessible, non-invasive, painless and cost-effective, single biochemical marker for assessing the severity of disease.

Key words: HIE**,** Perinatal asphyxia, APGAR score, urine uric acid, urine creatinine.

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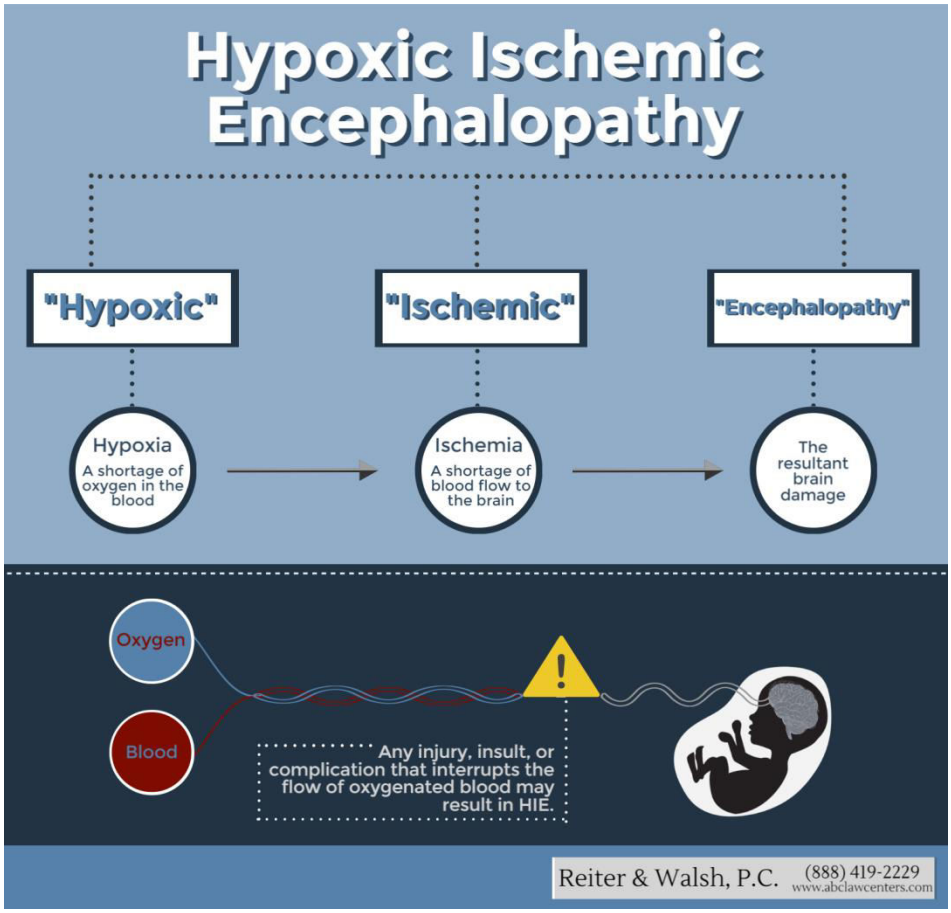
INTRODUCTION:

Perinatal asphyxia is a major cause of neonatal death world wide. Hypoxic ischemic encephalopathy is one of the leading cause of the neonatal mortality, it affects the tissues and it can lead to brain damage. Hypoxic ischemic encephalopathy results from due to lack of oxygen before, during or after birth. [1]



Globally, the prevalence of neonatal deaths accounts for 5.9 million child deaths occurred in 2015[2]. Perinatal asphyxia leading to HIE may result in adverse effects on all major body systems. Many of these complications are potentially fatal. [3] Neonatal hypoxia is one of the leading causes of neonatal mortality in developing countries. The prevalence of perinatal asphyxia in India, between 250,000 to 350,000 infants die each year due to perinatal asphyxia mostly within the first three days of life. In addition, antepartum and intrapartum asphyxia contributes to as many as 300,000 to 400,000 still-births. [4]

According to WHO, Perinatal asphyxia is defined as, "Failure to initiate or sustain breathing at birth"[5].Perinatal asphyxia occurs due to failure in fetal and newborn gas exchange. Hypoxic-ischemic encephalopathy (HIE) is the neurological manifestation of systemic hypoxia in new-born. The clinical criteria of Sarnat and Sarnat[6] measure the severity of HIE, classifying the patient in three stages according to level of consciousness, muscle tone, posture, tendinous reflexes, presence or absence of myoclonus and change of autonomic functions.

APGAR score is the most commonly used diagnostic and/or prognostic indicator to assess asphyxia in neonate. The 1-minute APGAR score indicates the need for immediate resuscitation. The change in score between 1 and 5 minutes is useful index for the effectiveness of resuscitative efforts. Due to some limitations, APGAR score alone does not predict neurologic outcome like cerebral palsy and as it is influenced by various factors like prematurity, fetal malformations, maternal medications and infection.[7]

To identify the perinatal asphyxia, many markers have been examined including low APGAR scores, cord pH, computed tomography (CT), electroencephalograms (EEG) and magnetic resonance imaging (MRI) scans and Doppler flow studies. Although there are many studies explored the mechanisms leading to neonatal asphyxia, for early determination of tissues due to birth asphyxia are still lacking. Hence, the present study was aimed (a) To estimate urinary uric acid and creatinine levels in spot urine sample.(b) To correlate the urinary uric acid, creatinine ratio with severity of hypoxic ischemic encephalopathy.

Stage	**Stage1(MILD)**	**Stage 2(Moderate)**	**Stage3(Severe)**
Level of consciousness	Hyper alert, irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control:	Uninhibited, over reactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Suck reflex	Uninhibited, over reactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Moro reflex	Normal	Mild hypotonia	Flaccid
Oculovestibular reflex	Normal	Overactive	Weak or absent
Tonic neck reflex	Slight	Strong	Absent
Autonomic function:	Generalized sympathetic	Generalized parasympathetic	Both systems Depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Seizures	None	Common focal or multifocal (6-24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic Findings	Normal (awake)	Early: generalized low voltage, slowing (continuous delta and theta) Later: periodic pattern (awake); seizures focal or multifocal; 1.0-1.5 Hz spike and wave	Early: periodic pattern with isopotential phases Later: totally Isopotential
Duration of symptoms	<24 hours	2-14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5-7 days	About 50% die; remainder with severe sequelae

MATERIALS & METHODS:

This prospective study conducted at Department of Paediatrics in collaboration with department of Biochemistry, RL Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Constituent of Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka. The study was approved by Institutional Ethical Committee and informed consent was obtained from the study subjects. A total of 108 term babies term with ≥37 weeks of gestations both inborn and out born babies with hypoxic ischemic encephalopathy as per Sarnat and Sarnat staging criteria were included in this study. Suspected babies with inborn errors of metabolism, babies with major congenital malformations were excluded from study as they may alter the uric acid and creatinine levels.

Detailed maternal history, birth events, APGAR score, sex of the baby and anthropometry of the baby were recorded on the proforma. Gestational age is assessed by New Ballard scoring system. Clinical and neurological examination was done for all the neonates. The babies who have suffered birthasphyxia and as per standard staging system (SARNAT AND SARNAT) which fit in to the criteria of Hypoxic Ischemic Encephalopathy be categorized in to stage 1, stage 2 and stage 3 were included in this study. The asphyxiated neonates were monitored for all components of SARNAT AND SARNAT staging in the immediate neonatal period in the NICU. Grading system used to grade the severity of HIE was SARNAT and SARNAT staging 1976.

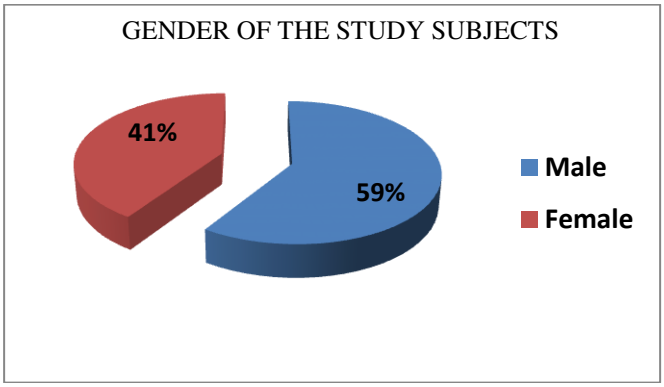
The neonates that were included in the study did not undergo therapeutic hypothermia before the collection of the urine samples. The urine samples were collected as early as possible from babies clinically diagnosed as HIE and all urine samples were collected by staff nurse in sterilized disposable urine bag and analyzed for urinary uric acid and creatinine. Urinary uric acid (uricase method) and urinary creatinine (sarcosine oxidase) was estimated by using dry chemistry auto analyzer Vitros FS 5.1.

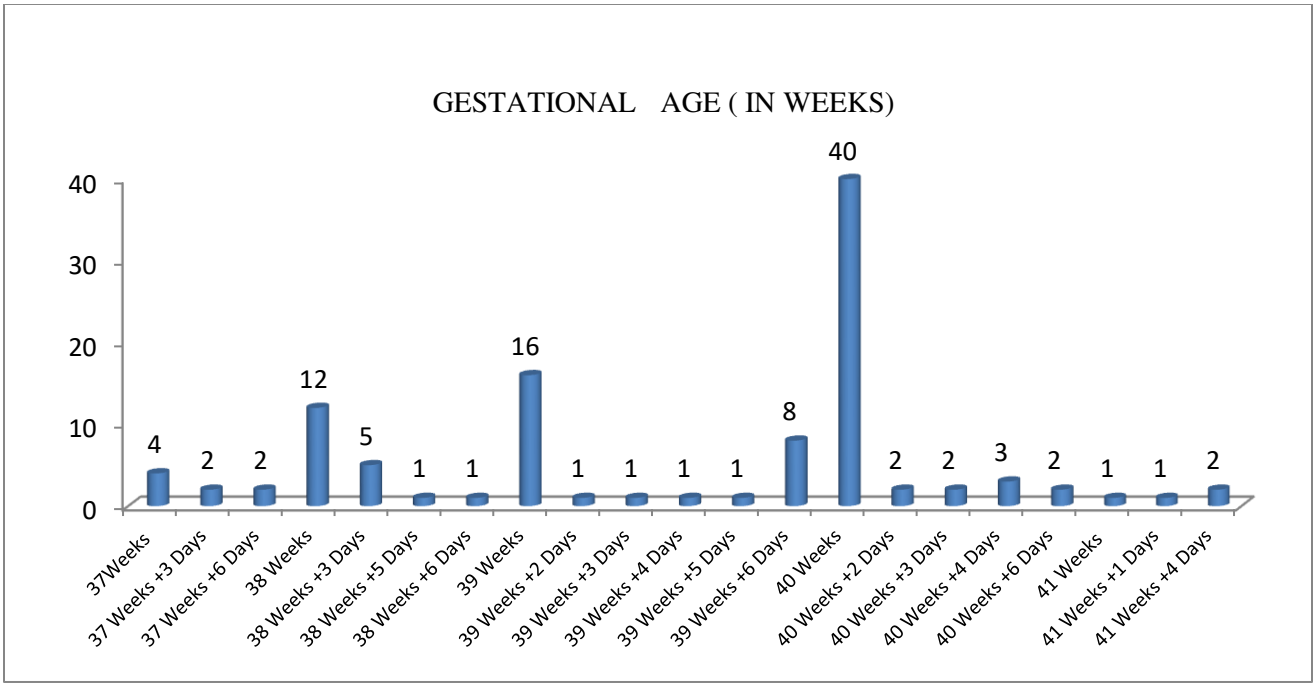
STATISTICAL ANALYSIS:

For none normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared across the study groups using Kruskal Wallis test and for correlation Pearson correlation was used. $P < 0.05$ was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

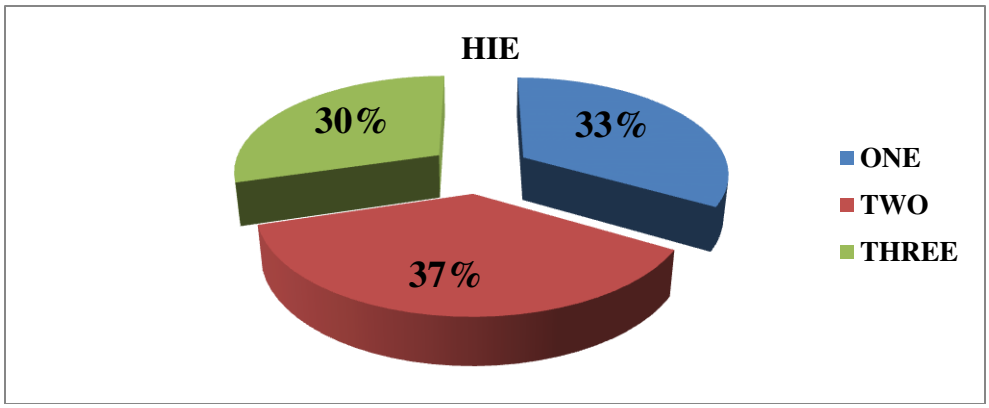
RESULTS:

In the present study, a total of 108 neonates were included in this study.



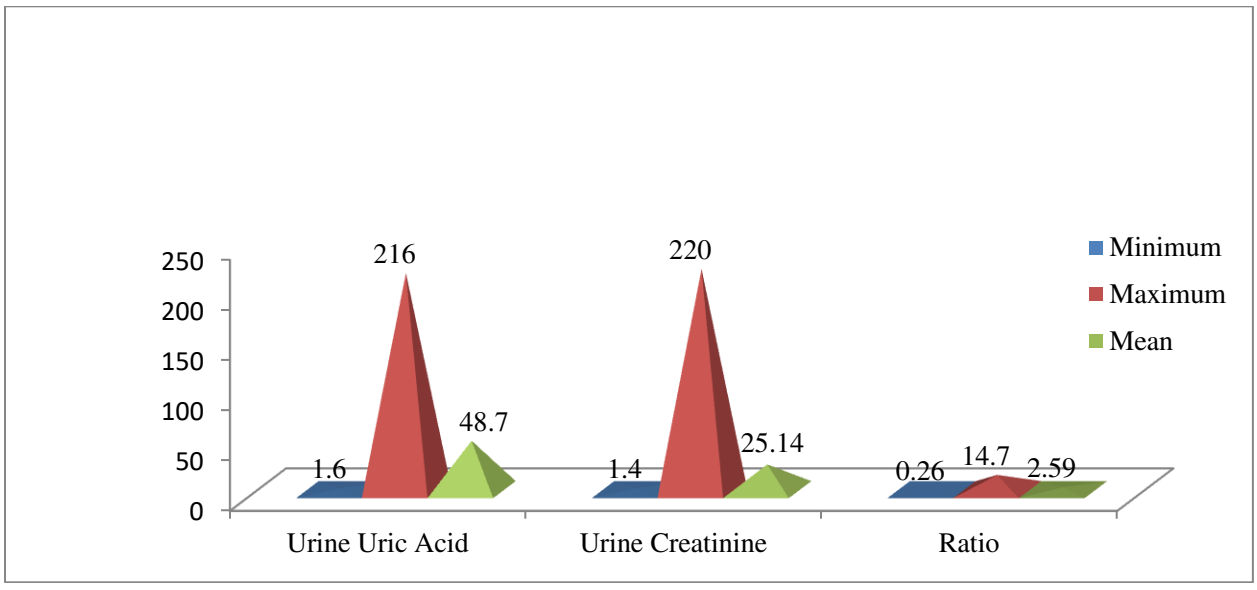


Anthropometric parameters were depicted in table1. Out of 108 subjects 36 (33.30%) subjects had HIE 1, 40 (37%) had HIE 2 and 32 (29.60%) had HIE 3.



Among the HIE 1 subjects, the median urine uric acid was 34 (17.25, 75.75), it was 38.20 (20.75, 57.50) subjects with HIE 2 and it was 35.50 (28, 60.45) among the subjects with HIE 3. The difference in the urine uric acid across HIE was statistically not significant (P Value 0.864).

Among the HIE 1 subjects, the median urine creatinine was 23.25 (14, 45.75), it was 16.90 (10, 31.25) subjects with HIE 2 and it was 10 (7.55, 15.05) among the subjects with HIE 3. The difference in the urine creatinine across HIE was statistically significant (P Value <0.001). Among the HIE 1 subjects, the median ratio was 1.26 (1.06, 2.20). it was 2.07 (1.87, 2.50) subjects with HIE 2 and it was 3.47 (2.85, 4.57) among the subjects with HIE 3. The difference in the ratio across HIE was statistically significant (P Value <0.001) as illustrated in table 2 and 3. A positive correlation was noted between severity HIE and urinary uric acid creatinine ratio with r =0.6 and statistically significant value p =0.001 noted.



APGAR score:

In the present study, the APGAR score was analysed for only the 59 children as most of the children were born outside. The mean APGAR score at 1 minute was 4.37 ± 1.11 in the study subjects, minimum level was 1 and maximum level was 7 (95% CI 4.08 to 4.66). The mean APGAR score 5 minutes was 6.25 ± 0.98 in the study subjects, minimum level was 3 and maximum level was 9 (95% CI 6 to 6.51). The mean APGAR score 10 minutes was 7.09 ± 1.1 in the study subjects, minimum level was 4 and maximum level was 9 (95% CI 6.79 to 7.39).

Parameter	Mean ± SD	Median	Min	Max	95% C.I	
					Lower	Upper
APGAR score 1 minutes	4.37 ± 1.11	4.00	1.00	7.00	4.08	4.66
APGAR score 5 minutes	6.25 ± 0.98	6.00	3.00	9.00	6.00	6.51
APGAR 10 minutes	7.09 ± 1.1	7.00	4.00	9.00	6.79	7.39

Table 1: Descriptive analysis of anthropometric parameters in study subjects

Parameter	Mean±SD
Birth weight (kg)	288±0.43
Head Circumference (cm)	33.11±0.96
Length (cm)	48.41±1.91

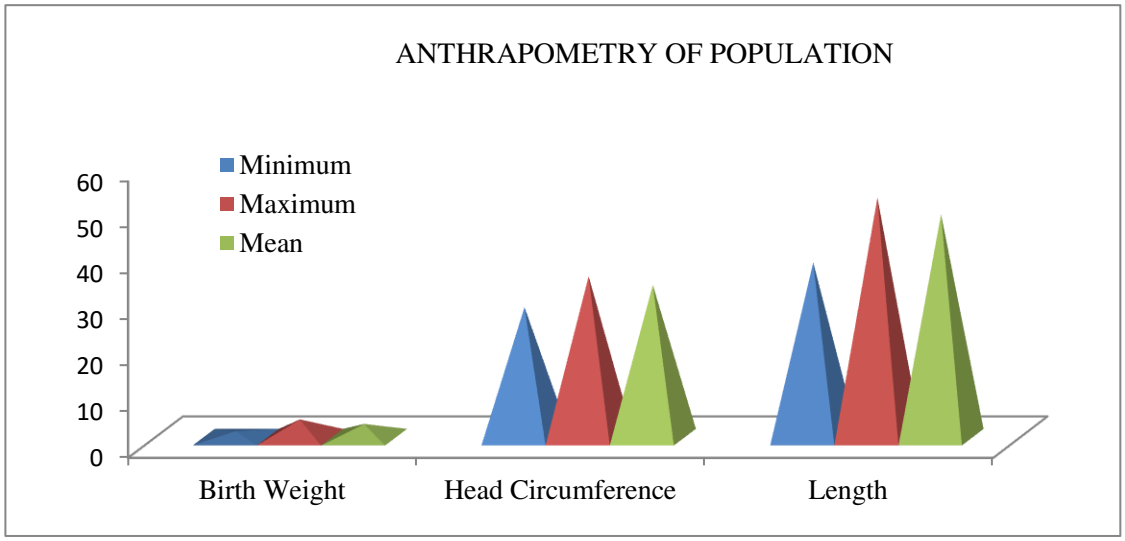
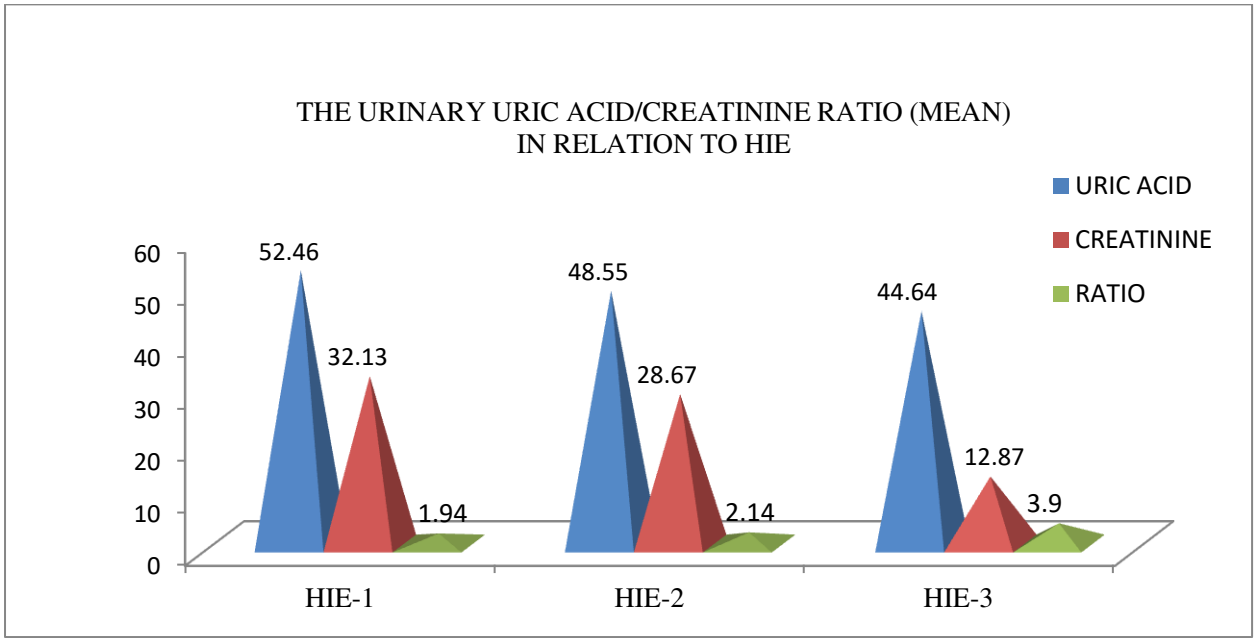


Table 2: Descriptive analysis of urine uric acid, creatinine and urine uric acid to creatinine ratio in study subjects

Parameter	Median	Interquartile Range
Urine uric acid	37.20	(22.25-61)
Urine creatinine	15	(10.29-75)
Urine uric acid/creatinine ratio (UCR)	2.20	(1.51-3.18)



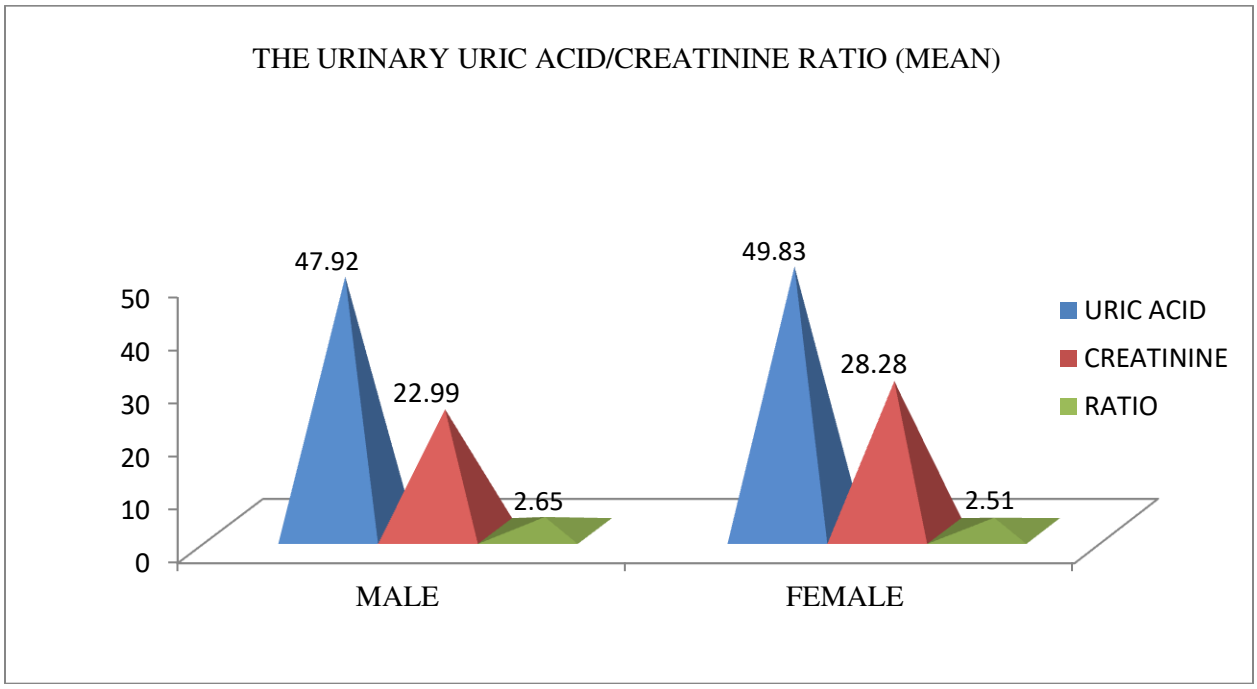


Table 3: Comparison of urine uric acid, creatinine and ratio across the HIE in the study subjects

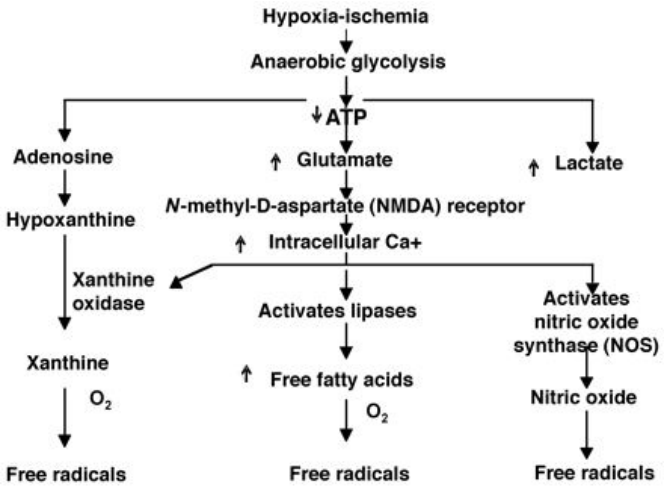
Parameter	HIE			P value
	1	2	3	
Urine uric acid Median (IQR)	34 (17.25-75.75)	38.20 (20.75-57.50)	35.50 (28-60.45)	0.864
Urine Creatinine Median (IQR)	23.25 (14-45.75)	16.90 (10-31.25)	10 (7.55-15.05)	<0.001
Ratio Median (IQR)	1.26 (1.06-2.20)	2.07 (1.87-2.50)	3.47 (2.85-4.57)	<0.001

DISCUSSION:

Perinatal asphyxia is one of the common neonatal problems, it significantly contributes to neonatal mortality and morbidity. To diagnose the perinatal asphyxia, there are various methods like cranial tomography, somatosensory evoked potentials and magnetic resonance tomography. But these modalities are not useful in first 24 h of life after birth. The APGAR score has a limited role in predicting the immediate outcome, such as that of HIE and the long-term sequelae[8].

Lawn et al, reported that the three most common causes of neonatal death are prematurity (28%), sepsis (26%) and asphyxia (23%) and is on the most commonest cause of still birth (45.1%) in India[9].

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.



Even though blood gas analysis remains the gold standard for establishing a diagnosis of newborn asphyxia, it is

invasive and increases the risk of infection. There are various parameters have been used to predict or define perinatal asphyxia like cord blood pH, meconium stained amniotic fluid, APGAR score. Investigation of haematological parameters and basic biomarkers helps in the diagnosis of newborn asphyxia. The prediction of mortality and morbidity for infants admitted to the NICU is the most important goal.

Chen et al. reported that the urinary UA/Cr ratio was remarkably higher in hypoxic premature infants than in hypoxic term infants[10].Bahubali et al,[11] reported that this ratio was elevated in neonates with birth asphyxia compared with the control group, and that this ratio was correlated significantly with the clinical severity of the disease. They also reported a significant negative correlation between this ratio and the Apgar score[10].

Hypoxia damages cerebral oxidative metabolism leading to an anaerobic glycolysis, yielding only 2 molecules of ATP as compared to 32 molecules of ATP during aerobic conditions. Prolonged hypoxia, causes further failure of oxidative phosphorylation and production of ATP. Decreased ATP and increased cellular destruction will cause an accumulation of Adenosine Monophosphate (AMP) and Adenosine Diphosphate (ADP), which will then get catabolized to its constituents of adenosine, inosine and hypoxanthine. Continuous tissue hypoxia and consequent reperfusion injury will result in hypoxanthine being oxidized to xanthine and uric acid in presence of the enzyme xanthine oxidase. This will increase the production of uric acid and cause it to enter blood from damaged tissues. This uric acid will then get excreted in urine where it can be easily detected. [12]

Urinary UA/Cr ratio is simple, non-invasive, painless and economical investigation for the diagnosis of perinatal asphyxia. Combined use of arterial blood pH, APGAR scores and UA/Cr ratio can help in early decision making about the level of care the new born requires. There have been very few studies from developing countries that have focused on this parameter[12].

Akisu, M et al [13] found in their study, the urinary uric acid creatinine ratios were found to be higher in asphyxiated infants (2.1 I 0.83) when compared with the controls (0.72 f 03). P < 0001).Urinary uric acid and creatinine ratio were significantly higher in infants with severe HIE (3.15 to 0.81) when compared with infants with moderate HIE (2.13 to 0.36: P< 0.01) and those with mild HIE (1.43 to 0.29: P < 0.001). The value of the urinay uric acid creatinine ratios of the mild and moderate HIE groups were also statistically different (P < 0.01). The results from the study by Banupriya, C, et al [14] the Spearman's correlation depicts that urine uric acid: creatinine ratio show a significant positive correlation with HIE staging and significant negative correlation with APGAR score.

Another study by Bader et al, [15] showed that Urinary uric acid and cratinine ratio was higher in the asphyxiated group when compared to controls. (2.06±1.12, vs. 0.64±0.48; P<0.001) which is also similar to our study. Our results are also supported by Chen et al., [16] who suggested that urinary ratio of UA to creatinine was significantly higher in both full term and preterm infants with perinatal asphyxia than in those without perinatal asphyxia.

Vandana et al.,[17] concluded in their study that the Urinary uric acid and creatinine ratio was significantly higher (P<0.0001) in asphyxiated babies (3.02±1.26) compared to control group (0.84±0.56). Mean values of urinary uric acid creatinine ratio in different stages of HIE showed increasing ratio with increasing stages of HIE (Table-III) with significantly higher ratios (P<0.0001) in stage II and III HIE (2.01±0.42 &4.24±0.79) compared to control group (0.84±0.56) and also compared to stage I HIE (1.23±0.52) (P<0.0001).

CONCLUSION:

According to the results of our study, urinary Uric Acid/Creatinine ratio is an accessible, non-invasive, painless and cost-effective, single biochemical marker for assessing the severity of disease and mortality. 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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