

Urinary Uric Acid/Creatinine Ratio as A diagnostic Marker for Perinatal Asphyxia

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ABSTRACT

Background: Brain injury that occurs during the perinatal period is one of the most commonly recognized causes of severe long-term neurological deficits in children often referred to as cerebral palsy (CP) that affects approximately 2-3 per 1000 school-aged children.

Objectives: The aim of this study was to detect the validity of urinary uric acid/creatinine ratio (UUA/Cr) in the identification of perinatal asphyxia and its role in grading asphyxia according to severity of hypoxic ischemic encephalopathy.

Patients and methods: This prospective study was carried out at Neonatology Unit or delivered at Gynecology Department of Zagazig University Hospitals during the period from July 2020 to July 2021. The study included 48 newborns with hypoxic ischemic encephalopathy (HIE). They were divided into two groups each group included (24) patients. Group I included 24 babies with perinatal asphyxia. Group II included 24 healthy babies (with gestational ages and weights matched to cases) as control group. The primary outcome was determining the values of UUA/Cr in newborns with hypoxic ischemic encephalopathy and its relation with different stages of HIE.

Results: UUA/Cr was significantly higher in cases as compared to control and was significantly higher in preterm babies when compared to full-term ones (this was applied for both cases and control). Moreover, significant difference in UA/Cr ratio in comparing the mild, moderate and severe groups of HIE.

Conclusion: We found that UA/Cr ratio level was increased in the asphyxiated newborns in comparison to normal healthy newborns.

Keywords: Apgar score, Hypoxic ischemic encephalopathy, Brain injury, Urinary uric acid/ creatinine ratio.

INTRODUCTION

Perinatal asphyxia is still one of the significant causes of mortality and long-term morbidity in spite of major advances in perinatal medicine. Failure to initiate or sustain respiration after birth” has been defined as criteria for the diagnosis of asphyxia by WHO. Perinatal asphyxia results in hypoxic injury to various organs including kidneys, lungs and liver but the most serious effects are seen on the central nervous system ⁽¹⁾. Anyway, asphyxia is considered one of the most preventable causes of morbidity and mortality so many asphyxiated babies might profit from appropriate and timely treatment and resuscitation when asphyxia is properly diagnosed ⁽²⁾.

It has been established that an Apgar score at 5 minutes is a better tool than 1 minute score for the assessment of newborn. However, the Apgar score is an expression of the infant’s physiological conditions and includes subjective components ⁽³⁾. The limitations of Apgar score have prompted researchers to explore into other molecular markers of organ damage. Studies suggest role of UUA/Cr in asphyxiated babies. Oxygen deficiency increases the level of hypoxanthines and uric acid due to degradation of purines, which are important sources of free radicals, which cause hypoxic brain injury ⁽⁴⁾.

This study aimed to detect the validity of UUA/Cr in the identification of perinatal asphyxia and its role in grading asphyxia according to severity of hypoxic ischemic encephalopathy.

PATIENTS AND METHODS

This study was carried out on 48 neonates admitted to Neonatology Unit or delivered at Gynecology Department of Zagazig University Hospitals during the period from July 2020 to July 2021.

Ethical approval:

Written informed consent was obtained from all participants’ parents and the study was approved by the Research Ethical Committee, Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Apgar score at 1 and 5 minutes ≤ 3 . Umbilical cord arterial pH < 7.2 . Umbilical cord arterial base deficit > 10 mEq/L. Postnatal clinical manifestations of CNS insult (e.g. seizures, lethargy, coma, abnormal tone and reflexes).

Exclusion criteria:

Cases of oliguria [urine output below 0.5 ml/kg/hour (estimated after the 2nd day) or abnormal renal functions (serum creatinine level above 1.25 mg/dl)]. These neonates were excluded to avoid misleading uric acid levels. Neonates who started oral milk feeding to avoid protein diet effect on increased uric acid excretion level. Cases with congenital anomalies.



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Asphyxiated cases (group A) were furtherly subdivided into three clinical stages of HIE:

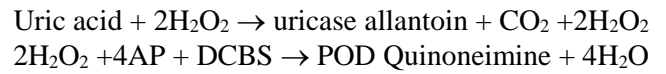
- HIE stage I (group 1): included hyperalertness, hyperreflexia and tachycardia.
- HIE stage II (group 2): included lethargy, hyporeflexia, bradycardia, hypotonia, weak suckling and Moro reflexes, and convulsions.
- HIE stage III (group 3): included stupor, profound hypotonia hypothermia and absent suckling and Moro reflexes.

All patients were subjected to detailed history taking: General and systemic examination including vital signs. Apgar scoring at 1, 5 and 10 minutes. Assessment of gestational age using new Ballard scoring system (5). Anthropometric measures at birth including baby's weight, length and head circumference. Meticulous organ system examination with special emphasis on neonatal reflexes, muscle tone and state of consciousness.

Laboratory investigation included:

Serum creatinine level: From postnatal venous sampling (cases with laboratory evidence of renal impairment were excluded from the study). Cord arterial blood gases and acid base balance were determined. At delivery, the umbilical cord was doubly clamped before the baby's first cry. Umbilical artery blood was collected into heparinized syringes for determination of pH, Pa O₂, Pa CO₂, HCO₃ and base deficit within 15 minutes of sampling using Rapid Lab 860. Serum sodium and potassium levels by Ion selective electrode method using clinical flame photometer and the samples used were the serum remaining after blood ultra- centrifugation. Urinary uric acid of first voided urine sample after admission was

obtained through application of a urine bag. The timing of the sample varied from one baby to another with a range of 2 to 24 hours. Determination of urinary uric acid was done by an enzymatic colorimetric test (uricase-PAP) by Spinreact. Test principle: uric acid was oxidized by uricase to allantoin and hydrogen peroxide, which under the influence of POD is oxidized to DCBS and 4-AP to form a red quinoneimine compound.



The quantity of this red quinoneimine is proportional to the uric acid concentration. Urinary creatinine was measured by using Jaffe method without de-proteinization. Measurements were done against air, at wavelength Hg 492 nm and spectrophotometer 490. Calculation: Concentration of creatinine in the sample was calculated: Creatinine concentration (mg/dl) = 100x A sample/A standard.

Radiological examination: MRI examination was done at Radiology Department, Zagazig University Hospital. Examination was done only to cases with moderate and severe HIE. CT was done during the first week of life.

Statistical Analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 27.0. Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables. The threshold of significance was fixed at 5% level (P-value). P value of ≤ 0.01 indicates highly significant results.

RESULTS

Table (1): Birth data of the studied groups

Variable		Cases (n=24)		Control (n=24)		MW	P
Age: (days)	Mean ± SD	4.08 ± 2.54		5.54 ± 2.75		1.96	0.07 NS
	Range	1 – 10		1-11			
	Median (IQR)	3 (2-6.5)		5(3.25-8)			
Variable		No	%	No	%	χ ²	P
Sex:	Male	12	50	14	58.3	0.34	0.56 NS
	Female	12	50	10	41.7		
Gestational Age: (weeks)	Mean ± SD	34.5 ± 1.82		35.42 ± 1.59		1.86	0.07 NS
	Variable	No	%	No	%		
Term:	Full term	19	79.2	18	75	0.12	0.73 NS
	Preterm	5	20.8	6	25		
Variable		Cases (n=24)		Control (n=24)		t	P
APGAR score: (5 min)	Mean± SD	2.46 ± 0.66		7.04 ± 1.16		16.84	<0.001**

SD: Standard deviation t: Independent t test χ²: Chi square test NS: Non-significant (P > 0.05)

Table (1) showed that there were no statistical significance differences between the studied groups regarding age, sex distribution, gestational age or term. Also there was a statistical significance decrease in Apgar score among cases compared to control group.

Table (2): Laboratory findings of the studied groups

Variable		Cases (n=24)	Control (n=24)	t	P
PH	Mean ± SD	7.19 ± 0.05	7.34 ± 0.17	t 4.34	<0.001**
Uric acid (mg/dl)	Mean ± SD	5.35 ± 0.47	0.52 ± 0.42	MW 5.84	<0.001**
Creatinine (mg/dl)	Mean ± SD	2.1 ± 0.37	0.44 ± 0.11	t 21.13	<0.001**
UUA/Cr	Mean ± SD	2.61 ± 0.46	1.20 ± 0.87	MW 4.60	<0.001**

SD: Standard deviation t: Independent t test MW: Mann Whitney test. **: highly significant (P < 0.001)

Table (2) showed that there was a statistical significance decrease in PH among cases compared to control group also there was a statistical significance increase in uric acid level, creatinine level and UUA/Cr among cases compared to control group.

Table (3): Relation between UUA/Cr and disease severity among cases group

Variable		No	UUA/ Creat		KW	P
			Median	IQR		
Severity:	Mild	8	2.13	1.86-2.48	15.19	<0.001**
	Moderate	9	2.67	2.58-2.72		
	Sever	7	3.13	2.68-3.18		

IQR: Inter quartile range KW: Kruskal Wallis test **: highly significant (P<0.001)

Table (3) showed that there was a statistical significance increase in UUA/Cr with increase disease severity.

Table (4): Validity of UUA/Cr in diagnosis of asphyxia among the studied groups and the cases group

Studied groups								
Cut off	AUC	CI 95%	P	Sensitivity	Specificity	PPV	NPV	Accuracy
>2.13	0.89	0.78-1	<0.001**	91.7%	83.3%	84.6%	90.9%	87.5%
Cases group								
Cut off	AUC	CI 95%	P	Sensitivity	Specificity	PPV	NPV	Accuracy
>2.87	0.87	0.73-1	<0.001**	85.7%	76.5%	60%	92.9%	79.2%

AUC: Area under curve CI: Confidence interval PPV: Positive predicted value NPV: Negative predicted value **: Highly significant (P < 0.001)

Regarding the studied groups, table (4) showed that at cut off > 2.13 UUA/creatinine ratio had sensitivity of 91.7%, specificity of 83.3% and accuracy of 87.5% in diagnosis of asphyxia. While, the cases group showed that at cut off > 2.13 UUA/creatinine ratio had sensitivity of 85.7%, specificity of 76.5% and accuracy of 79.2% in diagnosis of sever asphyxia.

DISCUSSION

Brain injury that occurs during the perinatal period is one of the most commonly recognized causes of severe long-term neurological deficits in children often referred to as cerebral palsy (CP) that affects approximately 2-3 per 1000 school-aged children⁽⁶⁾. The overwhelming evidence suggests that the proportion of

CP attributed to birth asphyxia represents about 10-20% of all cases⁽⁷⁾. However, this is the most relevant and important group of infants with CP because therapeutic strategies aimed to minimize or prevent cerebral injury are feasible⁽⁸⁾. The diagnosis of perinatal asphyxia, however, is often inexact and objective means of assessing its severity are controversial or often lacking. The use of fetal heart monitoring, blood gas analysis, Apgar score and other indicators of tissue damage have all failed to predict late neurological sequelae accurately⁽⁹⁾.

Our current study aimed at the detection of urinary UA/Cr ratio in asphyxiated neonates and its validity in assessing severity of HIE and its correlation to prognosis.

Our study agrees with, **Changlian et al.** ⁽¹⁰⁾ who found no significant sex difference between HIE patients and control. Also our study agrees with **Ballard et al.** ⁽⁵⁾ study. However, male sex predominance among newborns with perinatal asphyxia was evident in many previous studies, **Majeed et al.** ⁽¹¹⁾ and **Hill and Fitch** ⁽¹²⁾ who found that approximately 60% and 64% of asphyxiated neonates respectively were males. This finding was explained by **Greenough et al.** ⁽¹³⁾ who found that male fetuses are known to have lower catecholamine levels than their female counterparts and so are less protected against intrapartum hypoxia and its sequelae. Furthermore, **Lang and McCullough** ⁽¹⁴⁾ who were studying the different pathways of ischemic neuronal cell death and their relevance to sex reported that females are more protected from hypoxia than males by the neuroprotective effects of estrogen (17 β estradiol or E2) against ischemic insults. **Mc Cullough and Hurn** ⁽¹⁵⁾ and **Brann et al.** ⁽¹⁶⁾ found that there is more genetic predisposition to hypoxic-ischemic injuries in males compared to females.

Our study demonstrated that there was no significant relation between gender difference and brain insult, this is matching with **Volpe** ⁽¹⁷⁾.

Nelson et al. ⁽¹⁸⁾ recorded that preterm newborn mammals exhibit greater resistance to cerebral damage from hypoxic-ischemic insults than term newborns. But, this is controversial to **Song et al.** ⁽¹⁹⁾ who recorded higher incidence of asphyxia in deliveries ending prematurely. This difference may be explained by less liability to birth trauma and obstructed labour in preterm. Anyhow, a study on larger number of cases should be done to clarify this point.

In our study, mean birth weight difference was insignificant between cases and controls ($1.84 \pm .030$ in the former versus 1.99 ± 0.24 in the later). This is in agreement with **Fatrakul et al.** ⁽²⁰⁾. **Lee et al.** ⁽²¹⁾ did not record significant difference in birth weight between asphyxiated and normal newborns. On the contrary, **Chandra et al.** ⁽²²⁾ found that asphyxia is more incident in low birth weight (LBW) and explained this by the reduced ability of LBW infants to adapt during asphyxia due to low metabolic reserves.

Apgar score at 5 min (reflecting severity of asphyxia despite resuscitative measures) was lower in asphyxiated as compared to control (2.46 ± 0.66 versus 7.04 ± 1.16). This is in agreement with **Ehrenstein et al.** ⁽²³⁾, **Salustiano et al.** ⁽²⁴⁾ and **Biswas et al.** ⁽³⁾ who stated that 5 (not 1) minutes Apgar score is valid as an index for asphyxia.

On the contrary, **Sitthivuddhi et al.** ⁽²⁵⁾ found that normal umbilical pH (thus excluding asphyxia) occurred in 77.8% of depressed newborns (low Apgar) and 1% of vigorous babies had umbilical cord arterial acidemia. The mean cord arterial pH was significantly lower in cases than in control. This is in agreement with **Fatrakul et al.** ⁽²⁰⁾ who stated that profound acidemia is the hallmark of asphyxia. **Finer et al.** ⁽²⁶⁾ found that only pH values below 7.04 denote neurologic compromise. Moreover, they stated that normal pH correlates with

absence of any immediate or long-term neonatal morbidity. Also, **Goodwin et al.** ⁽²⁷⁾ found that HIE occurred in 12% of their studied group at low pH of 6.9-7.0.

Base deficits showed significantly higher levels in cases as compared to controls (7.19 ± 0.05 versus 7.34 ± 0.17). This is in accordance with **Low** ⁽²⁸⁾ who reported high values of base deficits and stated that a value of 10-19 mEq/L does not have any sequelae and at least values of more than 20 mEq/L are required to cause neurological damage. During asphyxia, in spite of the fall in blood and tissue pH and partial oxygen pressure, tissue oxygen consumption persists leading to further decrease in PaO₂ ⁽²⁹⁾.

Anaerobic metabolism ensues with the resultant production of large quantities of metabolic degradation products such as lactic acid. In parallel, ATP degradation is accelerated with increase in the formation of hypoxanthine ⁽³⁰⁾. In cases of continuing hypoxia, hypoxanthine is degraded by xanthine oxidase to xanthine and uric acid ⁽³¹⁾. As uric acid is the main metabolite of ATP degradation, so increased excretion of uric acid can be caused by metabolic changes reflecting cellular hypoxia or by renal changes ⁽³²⁾.

This study shows that the urinary UA/Cr in the early void urine sample was elevated in asphyxiated neonates as compared to normal (2.61 ± 0.46 in the former versus 1.20 ± 0.87 in the later). This is in agreement with the results of **Bhongir et al.** ⁽³³⁾ and **Basu et al.** ⁽³⁴⁾. But they conducted their work only on full term babies.

In our study urinary uric acid excretion in mg/dl GFR (Simkin index) was also higher in preterm normal neonates as compared to term babies. This is in agreement with **Bhongir et al.** ⁽³³⁾ who concluded that the more the prematurity the higher the urinary levels of uric acid. This was explained by **Basu et al.** ⁽³⁴⁾ as they speculated that uric acid may be physiologically important as an antioxidant in the epithelial lining fluid of the respiratory tract in preterm neonates during the first weeks of life.

In our study we found that urinary UA/Cr to be sensitive (91.7%), specific (83.3%), of good positive predictive value (84.6%) and accurate (87.5%) in the assessment of perinatal asphyxia. The urinary uric acid/creatinine ratio allows for the 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. While numerous indicators for asphyxia are recognized, no single indicator has been found to be predictive of subsequent morbidity. The Apgar score have historically been used to define asphyxia and attempt outcome prognostication but proved to be inaccurate ⁽³⁵⁾.

Although several biochemical indicators of asphyxia, such as hypoxanthine, brain isoenzyme of creatine phosphokinase, neuron specific enolase, excitatory amino acids, erythropoietin and vasopressin, have been reported, they are most useful as research goals and are not available in most clinical services.

However, we found UUA/Cr ratio to be a good, simple screening test for the early assessment of perinatal asphyxia. Furthermore, there was a correlation between this ratio and the severity of the encephalopathy and outcome indicating the degree of injury at an early stage when other quantitative methods frequently cannot be carried out.

CONCLUSION

We found that UUA/Cr level was increased in the asphyxiated newborns in comparison with normal healthy newborns. So, we conclude that UUA/Cr could be a useful marker for early diagnosis of HIE in the newborns and also in determining the grade of hypoxia. UUA/Cr was found to be very specific in predicting severity of injury. This specificity of UUA/Cr is a reflection of its nature as a marker of ischemia. Therefore, early prediction of HIE can protect asphyxiated neonates from permanent neurological damage and decrease mortalities from HIE.

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