EARLY BIOCHEMICAL PREDICTORS OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY AFTER PERINATAL ASPHYXIA

By

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ABSTRACT

Background: *Hypoxic-ischemic encephalopathy (HIE) is a common and serious disease of newborns leading to long term consequences.*

Objectives: *To investigate the possibility of using blood Lactate Dehydrogenase (LDH), Creatine Kinase muscle-brain and brain fractions (CK-MB, CK-BB) and Serum lactate levels as an early predictors for neonatal HIE and its severity even before the appearance of full clinical features to initiate early proper management.*

Patients and Methods: *A prospective case control study conducted on newborn infants admitted to the neonatal intensive care unit of Military Hospital–Wadi Aldawasir-KSA from January 2016 to January 2018. Thirty full term patients were enrolled to the study with documented perinatal asphyxia in addition to twenty full-term healthy newborn infants with no signs of birth asphyxia and an uneventful course during pregnancy and postnatal life as a control group. Full history taking, thourough clinical examination and routine laboratory tests in addition to biochemical markers (LDH, CK-MB, CK- BB and Serum lactate) were taken from all the babies within 15 min, then at 24 hrs. and 48 hrs. after birth.*

RESULTS: *The mean CK-MB level was 84.021 ± 39.24 U/L in asphyxiated group and 37.094 ± 14.76 U/L in the control group, with a statistically significant difference and P value <0.001, while the mean LDH value was (867.69 ± 372.61 U/L and 348.72 ± 112.61 U/L in both groups respectively) with a statistically significant difference and P value <0.001. A similar statistically significant difference found between both groups regarding Mean CK-BB and Serum Lactate. Among the asphyxiated group, the cut-off CK-MB value of (>90.4 U/L) had sensitivity of (27.3 %), specificity of (99%), positive predictive value of (99%) and negative predictive value of (59.4%), while the cut-off LDH value of (>540 U/L) has (90.24%) sensitivity, (93.89%) specificity, (90.36%) positive predictive value and (94.32%) negative predictive value. The predictive values of these biochemical markers in determining neonatal HIE and stages of severity were assessed.*

Conclusion: *LDH, CK-MB, CK-BB and Serum Lactate are useful biomarkers for early detection of HIE and if done routinely at the first few hours after birth for clinically suspected cases - even before appearance of full clinical signs - it will lead to early*

detection and initiation of managment aiming to improve the outcome. LDH is more sensitive but less specific biomarker while CK-MB has higher specificity and lesser sensitivity for perinatal hypoxic brain injury. The diagnostic performance of LDH seemed to be better than CK-MB in the newborns with perinatal asphyxia.

Key words: *Newborn, Hypoxic-Ischemic Encephalopathy, LDH, CK- BB, CK- MB, Lactate.*

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is the most severe complication of birth asphyxia. It's a major cause of neonatal morbidity and mortality and the third most common cause of neonatal death (23%), especially in the developing countries, after preterm birth (28%) and sepsis (26%). **(Prithviraj et al., 2016)**.

All the body organs can be affected by the asphyxia, leading to multiorgan dysfunction. In addition to pulmonary, renal, and cardiac dysfunction, anaerobic glycolysis and lactic acidosis, but hypoxic brain insult is of most concern and the least likely to heal completely with the most common sequelae of HIE **(Sato et al., 2008)**.

Early diagnosis of HIE is a challenging because the manifestations of asphyxia overlap with other illnesses, infants may present with non-specific symptoms and HIE is not always caused by a sentinel event. So, neonatologists and obstetricians are not always able to recognize brain insult in infants who suffer partial asphyxia at birth **(Shah and Perlman, 2009)**.

All methods of classification and staging of HIE like the Sarnat and Sarnat classification, the Thompson scoring and the Levene's classification are based on the clinical features and the outcome varies with the severity of HIE, as in moderate and severe stages the risk of death or neurologic sequelae increases greatly. Full neurological manifestations can take up to 72 hours to appear and management of HIE is done promptly after classification and staging. But by then, most of the damage has already set in **(Avijit et al., 2016)**.

Therapeutic hypothermia is the only promising medical treatment with long term neurodevelopmental results; however, it is effective only if it is administered in the early postnatal period. **(Heljic et al., 2018)** Thus, searching for early diagnostic tests and predictors to identify infants who will be at high risk for HIE within the short therapeutic

window (first few hours of life) can facilitate to provide early appropriate levels of care on arrival to NICU **(Patron-Chí et al., 2018)**.

Multiorgan dysfunction resulting from HIE can leads to leakage of intracellular enzymes from the injured cells – like lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), Creatine kinase muscle-brain fraction (CK-MB) and evaluation of these enzymes may be used as potential predictors to detect neonatal HIE and to grade its severity **(Perlman et al.,1989) (Shah and Perlman, 2009)**.

These biochemical markers that can be used in determining the HIE stage before appearance of clinical manifestations of the disease will be of great value and the rate of change in the serum levels of these intracellular enzymes in the first few hours of extrauterine life may serve as an indication of high risk for the development of HIE **(Beken et al., 2014)**.

A primary goal of biomarkers is to identify injury and predict long-term outcomes, so, variety of biomarkers have been essential topics in HIE research and examined to identify perinatal hypoxia and its complications **(Sachin et al., 2019)**.

Ideally, biomarkers that could be collected shortly after birth, having high accuracy rate and of low cost and feasibility will help in appropriate early management especially in developing countries **(Graham et al., 2018)**.

Our objectives were to investigate the possibility of using the serum levels of these biomarkers (LDH, CK-MB, CK-BBand Serum lactate) as an early predictors for neonatal HIE and its severity, even before the appearance of full clinicalfeatures to initiate early proper management.

Ethical Considerations: Approval of Institutional Ethical Committee (IEC) and written consent from parents were obtained before the study. The parents had the right to refuse to share in the study. All the data of the study are confidential and the patients had the right to keep them. The authors received no financial support regarding the study or publication and claimed that, no conflict of interest regarding the study or publication.

PATIENTS AND MATERIALS

A prospective case controled study conducted on newborn infants admitted to the neonatal intensive care unit (NICU) of

Military Hospital–Wadi Aldawasir-KSA during the period of January 2016 to January 2018.

All Fullterm (>37 Wks) newborns with signs of birth asphyxia who fulfilled any of the following criteria were included in the study:

A. Intrapartum signs of fetal compromise, e.g; non-reassuring non-stress test on continuous electronic fetal monitoring or meconium staining of the amniotic fluid.
B. Persistence of an APGAR score 0–3 for more than 5 minutes.
C. Profound metabolic or mixed acidemia (pH <7.10) in an umbilical artery blood sample.
D. Neurological abnormalities in the immediate neonatal period e.g; seizures, hypotonia or coma.
E. Evidence of multiorgan system dysfunction in the immediate neonatal period e.g; oligo-anuria.
F. Mild, moderate, or severe HIE, as defined by Sarnat and Sarnat staging. **(Sarnat and Sarnat, 1976)**.

Prematures <36 weeks gestational age or birth weight less than 2 Kg, major congenital malformation, , metabolic or chromosomal abnormalities, septic shock, or if the mother received opioids or magnesium sulfate within 4 h before delivery were excluded from the study.

Thirty full term patients as per criteria were enrolled in the study as the asphyxia group in addition to twenty full-term healthy neonates with uneventfull perinatal history, no maternal illness, arterial blood cord pH >7.2, Apgar score of >7 after 5 minutes and normal physical examination as a control group.

Full history taking including demographic data, such as gestational age (assessed by last menstrual date then by New Ballard score), birth weight and risk factors for perinatal asphyxia were recorded, followed by thorough clinical and neurological examination for all the neonates included in the study. The asphyxiated patients were stratified into three groups (Mild, Moderate, and Severe) on the basis of the clinical features by Sarnat and Sarnat staging system **(Sarnat and Sarnat, 1976)**. All asphyxiated babies immediately resuscitated and recieved full medical care, including therapeutic hypothermia for patients with moderate and severe hypoxia.

After admission to NICU, blood samples were collected from all babies within 15 min, then at 24 hour and 48 hour after birth. Immediately after sampling, the blood in the tubes was placed on a mixture of water and ice to ensure a constant temperature of 4°C then analyzed for cord arterial blood gases (ABG) (pH, HCO3, base deficit levels), routine investigations including; complete blood count (CBC), renal parameters (blood urea nitrogen [BUN], and creatinine), liver parameters (aspartate transaminase (AST), alanine transaminase (ALT), prothrombin time/international normalized ratio [PT/INR]), electrolyte levels and C-reactive protein (CRP) in addition to biochemical markers (LDH, CK- MB, CK- BB and Serum lactate).

Serum levels of biomarkers (CK-MB, CK-BB and LDH) determined by enzyme-linked immunosorbent method on enzyme-linked fluorescent assay by a biochemical analyzer HITACHI Roche – Cobas 6000. Blood lactate levels analyzed by a gas analyzer Abbott ABL 800 Basic Plus. Serum concentration of CRP was determined at 25°C by the biochemical analyzer HITACHI Roche – Cobas C 501. The reference value in the clinical lab of AFHWD was irrespective of age is < 6 mg/dL. The predictive values of these biochemical markers in determining neonatal HIE and stages of severity were assessed.

Statistical analysis done by Statistical Package for Social Sciences (SPSS, Chicago, IL, U.S.A.) program (Version 20).

Continuous variables are shown as a descriptive statistics; mean value ± standard deviation (SD) and median (min; max) if they had symmetric or asymmetric distribution respectively. Correlations were calculated by the Spearman rank method. Sensitivity, specificity, PPV and NPV for development of moderate or severe asphyxia were obtained using optimal cut-off levels and were calculated on the material used in our study. Probability values (P-value) <0.05 were considered to be significant. The suitability of numeric variables was tested using receiver operating characteristic (ROC) curves and assessed using the areas under the curves.

RESULTS

Thirty full term neonates were enrolled to our study. Twenty control neonates were selected and sampled in the course of routine neonatal screening. This work was done in a tertiary care hospital with a neonatal intensive care facility. All blood investigations done within 15 minutes, at 24 hours and 48 hours after birth for serial measurements.

According to the classification of **(Sarnat and Sarnat, 1976)**, asphyxiated patients were stratified into three groups; mild 16 (53.33%), moderate 9 (30%) and severe HIE 5 (16.67%) patients.

Patients with HIE were classified into two groups; Mild hypoxic group (16 patients; 53.33%) and moderate/severe hypoxic group (14 patients; 46.67%) for statistical correlation.

There was no difference in demographic data between asphyxiated and control groups, where both groups were statistically similar in gender distribution, mode of delivery, mean gestational age and birth weight, but the difference was statistically significant as regards Apgar score at 1 and 5 minutes and meconium stained liquor. Interestingly from all asphyxiated babies (13.3%) showed meconium stained liquor; (75%) of them had moderate /severe HIE. **(Table I)**.

Table (I): Demographic data of studied neonates

Data	Control group (n=20)	Mild Hypoxia (n=16)	Mod / Severe Hypoxia (n=14)	*p* value
Gestational age (wks.)	38.134 ± 2.14	38.45 ± 1.68	39.11 ± 1.42	0.71 #
Sex (M/F)	8/12	9/7	6/8	0 .24 #
Birth weight (gms)				
Mean (+/- SD)	3346.19 ± 368.71	3267.00 ± 471.62	3425 ± 327.21	0 .18 #
Mode of delivery				0 .63 #
Cesarean section	12	7	8	
Spontaneous vaginal	8	9	6	
Apgar score (1 min)	7.63 ± 0.81	5.03 ± 1.54	4.01 ± 1.36	0.001 *
(5 min)	9.31 ± 0.68	7.68 ± 0.79	6.08 ± 0.86	0.001 *
Meconium stained liquor				
n = 4 (13.3%)	**0/20 (0%)**	**1/16 (6.25%)**	**3 /14 (21.4%)**	**0.001***

- ***P*** values are for comparison between control(n=20) and asphyxiated infants(n=30). *Significant at p<0.05 #Non-significant.

No statistically significant difference was detected between both asphyxia and control groups and even among all the stages of HIE with regard to Hb, WBCs, CRP, BUN and glucose values **(Tables II)**.

Table II: Comparison of routine investigations between mild and moderate/severe hypoxia groups

Serum marker	**Mild hypoxia group** (n=16) (Mean ±SD)	**Mod/Severe Hypoxia group** (n=14) (Mean ±SD)	***P* Value**
Hb			
Admission	16.8±3.4	17.3±2.5	0.446
24 hours	17.4±2.5	18.1±3.2	0.354
48 hours	17.1±3.3	17.9±1.6	0.408
WBC			
Admission	21307±3587	25214±5421	0.187
24 hours	18342±2542	21548±3457	0.231
48 hours	17548±1457	19634±7458	0.354
Platelets (X 1000)			
Admission	201.015±33121	120.141±43124	0.001*
24 hours	214.226±42153	115.671±32547	0.001*
48 hours	226.118±38241	141.305±42548	0.001*
CRP			
Admission	0.29±0.41	0.43±0.35	0.461
24 hours	0.34±0.22	0.46±0.27	0.537
48 hours	0.33±0.35	0.41±0.12	0.498
Glucose			
Admission	61±7	57±3	0.435
24 hours	58±4	60±4	0.412
48 hours	62±5	63±1	0.624

*Significant at p<0.05 #Non-significant.

However, cord pH and base excess in addition to platelet counts were low, creatinine, SGPT and SGOT levels done on admission, at 24 h and 48 h were significantly higher in hypoxic group and in moderate/severe groups compared to the control and to mild groups respectively **(Table III)**.

Table III: Comparison of Renal and some liver functions between mild and moderate/severe hypoxia groups

Serum marker	Mild hypoxia group (n=16) (Mean ±SD)	Mod/Severe Hypoxia group (n=14) (Mean ±SD)	*P* Value
Cord blood pH			
Admission	7.12±0.10	7.08±0.12	0.001*
24 hours	7.35±0.06	7.22±0.09	0.001*
48 hours	7.37±0.03	7.29±0.04	0.001*
Cord blood BE			
Admission	−8.3±4.1	−15.2±3.1	0.001*
24 hours	−7.1±3.6	−13.1±1.7	0.001*
48 hours	−6.5±2.7	−9.2±2.	0.001*
Creatinine (in U/L)			
Admission	0.52±3	0.92±4	0.001*
24 hours	0.46±2	0.80±5	0.001*
48 hours	0.39±4	0.79±3	0.001*
BUN			
Admission	17±8	23±1	0.382
24 hours	18±5	22±4	0.411
48 hours	17±3	18±6	0.524
SGOT			
Admission	58±7	87±9	0.001*
24 hours	66 ±2	98±5	0.001*
48 hours	59 ±6	118 ±4	0.001*
SGPT			
Admission	51±3	93±8	0.001*
24 hours	48 ±5	99 ±4	0.001*
48 hours	38 ±7	78±9	0.001*

*Significant at p<0.05 #Non-significant.

A statistically significant difference between asphyxia and control groups and even between both hypoxia groups as regards admission, 24 hours and 48 hours levels of cardiac enzyme levels (CK- MB and CK- BB), LDH, and Lactate especially in infants with moderate/severe HIE **(Table IV)**.

Table IV: Comparison of Biochemical Markers between mild and moderate/severe hypoxia groups

Serum marker	Mild hypoxia group (n=16) (Mean ±SD)	Mod/Severe Hypoxia group (n=14) (Mean ±SD)	*P* Value
CK MB (in U/L)			
Admission	48.02±16.71	98.34±41.86	0.001*
24 hours	54.13±18.12	106.25± 62.44	0.001*
48 hours	59.04±12.47	114.21±58.13	0.001*
CK BB (in U/L)			
Admission	12.41 ± 8.91	26.19 ± 11.75	0.001*
24 hours	9.87 ± 5.84	18.87 ±10.15	0.001*
48 hours	10.21± 2.72	19.79 ±12.04	0.001*
LDH (in U/L)			
Admission	673.03±82.14	829.21±315	0.001*
24 hours	495.21±74.34	2098±234	0.001*
48 hours	549.46±85.05	2618±517	0.001*
Lactate (in U/L)			
Admission	4.2±0.3	7.7±0.4	0.001*
24 hours	5.1±0.6	12.3±0.2	0.001*
48 hours	3.8±0.4	9.6±0.3	0.001*

** Significant at p <0 .05, N = Number of cases, SD = Standard deviation.*

A comparison of mean values of biomarkers was undertaken between both control and asphyxia groups. It showed higher mean values of CK-MB, LDH, CK-BB and serum Lactate levels in neonates of asphyxia group with a statistically highly significant difference as compared to neonates of control group (P value <0.001) **(Table V)**.

Table (V): Comparison of mean values of biomarkers in neonates of both control and Asphyxia groups

Biomarker	Control group	Asphyxia group	P value
Mean CK-MB (U/L±SD)	37.094 ± 14.76	84.021 ± 39.24	<0.001
Range	(29.254 – 48.642)	(53.592 – 104.358)	
Mean LDH (U/L±SD)	348.72 ± 112.61	867.69 ± 372.61	<0.001
Range	(226.34 – 471.57)	(691.34 – 1028.49)	
Mean CK-BB (U/L±SD)	9.21 ± 3.1	19.32 ± 2.8	<0.001
Range	(6.82 – 12.44)	(17.61 – 22.35)	
Serum Lactate (U/L±SD)	3.1 ± 0.4	5.9 ± 0.3	<0.001
Range	(2.2 – 5.1)	(3.8 – 8.2)	

** Significant at p <0 .05, SD = Standard deviation.*

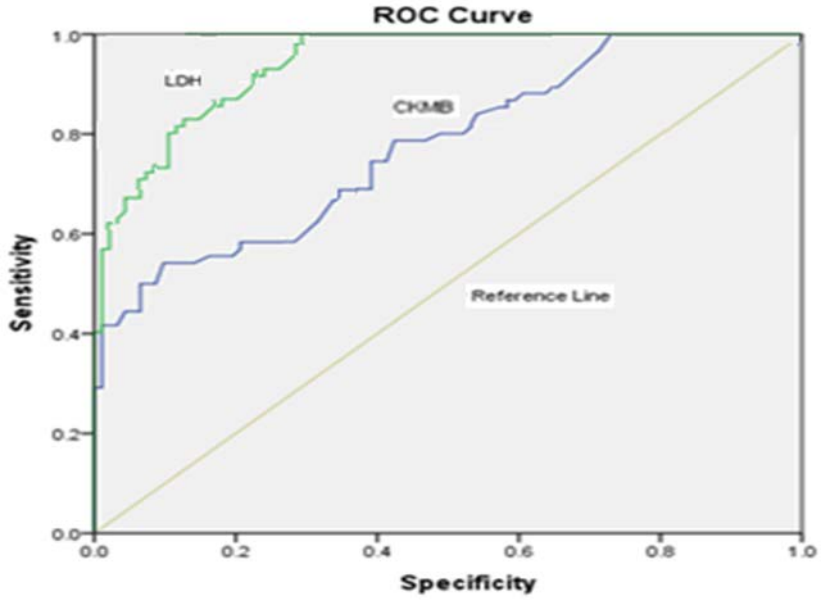
Among the asphyxiated neonates, the cut-off CK-MB value was (>90.4 U/L) with (27.3%) sensitivity, (99%) specificity, (99%) positive predictive value (PPV) and (59.4%) negative predictive value (NPV). The cut-off value of LDH was (>540 U/L) with (90.24%) sensitivity, (93.89%) specificity, (90.36%) PPV and (94.32%) NPV **Table (VI)**.

Table (VI): Sensitivity, Specificity and Predictive values of CK-MB and LDH values

Biomarker	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
CK-MB	(>90.4 U/L)	27.3 %	99%	99%	59.4%	0.763
LDH	(≥540 U/L)	90.24%	93.89%	90.36%	94.32%	0.894

AUC, area under the curve.

The Receiving Operating Characteristic (ROC) curve of both LDH and CKMB showed more area under ROC value for LDH when compared to CK-MB (0.894 vs. 0.763) as demonstrated in **Figure (1)**.



DISCUSSION

Perinatal asphyxia is a common cause of neonatal morbidity and mortality with subsequent neurologic disabilities among survivors. In addition to pulmonary, renal, and cardiac dysfunction, HIE develops in one third of asphyxiated newborns, where moderate and severe encephalopathy carry the risk of death or neurologic sequelae **(Nagdyman et al., 2001)**.

Early detection of infants at a high risk for brain damage soon after birth within the therapeutic window (the first few hours of life) and before clinical signs appear is highly important for initiation of the treatment to lessen the number of mortalities and morbidities. So, many investigators try to find sensitive biomarkers for brain injury in infants with HIE **(Heljic et al., 2018)**. Our results showed that both study groups are similar as regards demographic data, but when comparing both groups as regards Apgar score and pH there was highly statistically significant difference, which is expected in view of our selection criteria as hypoxic group with lower Apgar scores than the control group together with lower pH values due to global tissue ischemia and

concurrent metabolic or mixed acidosis.

Most of neonates with meconium stained liqour (75%) were from the moderate/severe hypoxia group, because systemic hypoxia-ischemia results in relaxation of fetal anal sphincter with meconium staining of amniotic fluid and potential risk of inhaled meconium that may lead to lung injury, compromised gas exchange or pulmonary hypertension of asphyxiated newborns that may need assisted ventilation **(Ferriero; 2004)**.

Moderate and severe hypoxia group showed a highly significant difference when compared to mild hypoxia group as regards thrombocytopenia, renal and hepatic dysfunction, this was in agreement with **(Prithviraj et al., 2016)**, as the hypoxic-ischemic insult causes direct organ damage with multisystem dysfunction including myocardium, brain, kidneys, liver and bone marrow. Bone marrow depression will lead to increase in nucleated RBCs and thrombocytopenia **(Ferriero; 2004)**.

Several studies have been conducted to evaluate better markers that can help to differentiate asphyxial and non-asphyxial etiology in neonates. In our study; the serum levels of biochemical markers; LDH, CK-MB, CK-BB and Serum lactate were examined with a statistically significant difference found between both study groups (Asphyxia and control) and both hypoxia groups. In accordance to our findings, the study of **(Prithviraj et al., 2016)**, reported a statistically significant elevation in LDH and cardiac enzyme levels (CK-MB and CK-BB) in children of severe HIE compared to babies from mild and moderate stages. The study of **(Perlman et al., 1989)** explained that HIE can leads to leakage of intracellular enzymes from the injured cells which signals multiorgan dysfunction and can be used as potential predictors to grade hypoxic ischemic injury in newborns with perinatal asphyxia.

In current study; the mean CK-MB and LDH values were higher in neonates of asphyxia group compared to the control group, with a statistically significant difference and P value <0.001. These findings matched the study of **(Avijit et al., 2016)** who studied 42 newborn with HIE versus 50 apparently healthy controls and they concluded that; there is statistically significant increase in levels of CK, UA, LDH and CK-MB within first 12 to 24 hours in an asphyxiated newborn infants suffering from

HIE compared to a normal newborns. Another study by **(Barberi et al; 1999)** reported that in an asphyxiated group CK, CK-MB, CK-MB/CK ratio and LDH were all increased compared to a respiratory distress group, in which only CKMB and the CK-MB/CK ratio were slightly elevated. In a retrospective study of the Japanese National Center conducted by **(Hayakawa et al; 2014)**, Serum levels of CK-MB and lactate at admission were significantly higher in infants with poor outcome compared to those with favorable outcomes.

The Mean values of CK-BB and Serum Lactate showed a statistically significant difference between asphyxia and control groups, in agreement with **(Lv et al., 2015)** who observed increased CK-BB and Lactate levels in a study reviewed the mechanism of neonatal hypoxic ischemic encephalopathy in relation to numerous brain-related biomarkers, and in accordance with **(Nagdyman et al., 2001)** who observed a significantly higher levels of serum CK-BB in infants with moderate or severe HIE when compared with infants with no or mild HIE at 2, 6, and 12 hours after birth.

Furthermore, **(Cuestas, 1980)** reported a rapid increase in serum CK-BB activity after birth in neonates with severe asphyxia and neurologic damage, whereas in healthy neonates, a rapid decline in this activity was significant and reaching a stable value after 6 hours to 5 days. Even in the era of therapeutic hypothermia (TH), a study conducted by **(Chiang et al., 2016)** revealed that; higher serum levels of lactate and LDH and abnormal results of brain MRI following TH are associated with poor neurodevelopmental outcome in neonates with HIE, matching the study of **(Shah et al; 2004)** who indicated that the highest recorded lactate level in the 1st hour of life and serial measurements of lactate were important predictors of moderate to severe HIE.

In our study, the cut-off value of CK-MB (>90.4 U/L) has (27.3%) sensitivity, (99%) specificity, (99%) PPV and (59.4%) NPV, which is comparable to the result of study conducted at CK-MB value (> 92.6 U/L) by **(Reddy et al., 2008)** with (36%, 100%, 100% and 52% respectively) and in agreement with the study of **(Primhak et al., 1985)** who observed that the absolute and percentage levels of CK-MB were higher in asphyxiated babies and it reached the maximum level at 8 hours and fell by 72 hours in both normal and asphyxiated neonates. Another

study monitored CK-MB activity in normal and severely asphyxiated neonates and reported a significantly higher CK-MB values with subsequent neurologic abnormality in 77% of severely asphyxiated neonates who survived the neonatal period **(Sachin et al., 2019)**.

The cut-off value of LDH (>540 U/L) has (90.24%) sensitivity, (93.89%) specificity, PPV (90.36%) and NPV (94.32%) in the studied newborns. This is comparable to **(Reddy et al., 2008)** with a cut-off value (>580 U/L) in which sensitivity, specificity, PPV and NPV were (100%, 89%, 92% and 100% respectively), while in **(Karlsson et al; 2008)** a cut-off level of 1049 U/L for LDH was the most suitable predictor of neonatal HIE with a sensitivity of 100% and specificity of 97% and in the study of **(Rajakumar et al., 2008)**, sensitivity and specificity of LDH were 56.5% and 75.7%. The variation can be attributed to the difference in inclusion criteria, sample size and percentage of severe hypoxia group in each study. Moreover; timing of the sample can play a role as explained by **(Patron-Chi et al., 2018)** who monitored serum LDH in asphyxiated newborn and concluded that; despite its significantly higher levels in asphyxiated neonates, there is a variable concentrations of LDH noticed during the first 12 hours of life compared to the non-asphyxiated group.

The diagnostic performance of LDH seemed to be better than CK-MB in the newborns with perinatal asphyxia as shown by the Receiving operating Characteristic (ROC) curve of both LDH and CKMB with more Area under ROC value for LDH when compared to CK-MB (0.894 vs. 0.763).

In developing countries with such poor resource settings; low cost and bed side diagnostic test having high sensitivity and specificity will help in early and proper management of newborns with perinatal asphyxia aiming to improve the outcome.

CONCLUSION

LDH, CK-MB, CK-BB and Serum Lactate are useful biomarkers in early detection of HIE and if done routinely at the first few hours after birth for clinically suspected cases before appearance of full clinical signs, It will help in early initiation of treatment for HIE patients. LDH is more sensitive but less specific biomarker while CK-MB has higher specificity and lesser sensitivity for hypoxic brain injury. The diagnostic

performance of LDH seemed to be better than CK-MB in the newborns with perinatal asphyxia.

Limitations of the study: The small sample size and inability to follow up for several years seem to be the main limitations in our study and we suggest that this study be conducted with a bigger sample size and over a longer duration to detect the neurological and developmental outcome for more promising results.

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المؤشرات البيوكيميائية المبكرة لاعتلال الدماغ بنقص التأكسج الإقفاري بعد اختناق ما حول الولادة

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المقدمة والهدف من البحث: اعتلال الدماغ بنقص التأكسج الإقفاري هو مرض شائع وخطير لحديثي الولادة يؤدي إلى عواقب طويلة المدى. وهدفت الدراسة الى التحقيق في إمكانية استخدام مؤشرات بيوكيميائية مبكرة مثل لاكتات الدم الغير مهدرجة ، كيناز الكرياتين للعضلات (CK-MB)- كيناز الكرياتين للدماغ (CK-BB) ومستويات اللاكتات بالمصل (Serum Lactate) كمتنبئين مبكرين لاعتلال الدماغ بنقص التأكسج الإقفاري وشدته لدى حديثي الولادة -حتى قبل ظهور السمات السريرية الكاملة- للسماح بالتدخل السريع والفعال في وقت مبكر.

المرضى و طرق البحث: دراسة قائمة على الملاحظة أجريت على الأطفال المنومين بوحدة العناية المركزة لحديثي الولادة. وتم تسجيل ثلاثين مريضًا في هذه الدراسة من مكتملي العمر الرحمي ومصابين بالاختناق في فترة ما حول الولادة بالإضافة إلى عشرين طفلا حديثي الولادة ممن لا تظهر عليهم علامات اختناق الولادة ولا علامات خطورة أثناء الحمل وما حول الولادة ومشابهة بالوزن والعمر الرحمي كمجموعة ضبط صحية. تم أخذ المؤشرات الحيوية والاختبارات المعملية الروتينية الكاملة بالإضافة إلى لاكتات الدم الغير مهدرجة (LDH)، كيناز الكرياتين للعضلات والدماغ (CK-MB)- كيناز

الكرياتين للدماغ (CK-BB) و مستويات اللاكتات بالمصل (Serum Lactate) من جميع الأطفال في غضون 15 دقيقة، ثم في 24 ساعة و 48 ساعة من الدخول إلى وحدة حديثي الولادة.

النتائج: أظهرت الدراسة ان متوسط مستوى كيناز الكرياتين للعضلات (CK-MB) في حديثي الولادة من مجموعة المرضى كان (CK-MB 84.021±39.24 وحدة / لتر) بينما كان في المجموعة الضابطة (14.76±37.094 وحدة / لتر) مع وجود فرق معتد به إحصائياً بين المجموعتين. بينما كان متوسط قيمة لاكتات الدم الغير مهدرجة (LDH) ذات دلالة إحصائية عند حديثي الولادة من مجموعة المرضى مقارنة بحديثي الولادة من المجموعة الضابطة (867.69 ± 372.61 وحدة / لتر في مجموعة المرضى و 348.72 ± 112.61 وحدة / لتر في مجموعة الضبط). كما وجد فرق ذو دلالة إحصائية مماثلة بين المجموعتين فيما يتعلق بمتوسط كيناز الكرياتين للدماغ (CK-BB) ومستوى اللاكتات بالمصل (Serum Lactate). ومن بين حديثي الولادة الذين تمت دراستهم، كان قيمة مستوى كيناز الكرياتين للعضلات (CK-MB) المقطوعة ذات حساسية (27.3٪) مع خصوصية (99٪). وقيمة تنبؤية إيجابية تبلغ (99٪) وقيمة تنبؤية سلبية تبلغ (59.4٪).بينما كانت قيمة لاكتات الدم الغير مهدرجة (LDH) المقطوعة ذات حساسية (90.24٪) مع خصوصية (93.89٪) وقيمة تنبؤية إيجابية تبلغ 91.67٪ مع قيمة تنبؤية سلبية تبلغ 93.48٪ من حديثي الولادة المشمولين بالدراسة.

ونخلص من هذه الدراسة الى أن: لاكتات الدم الغير مهدرجة (LDH)، كيناز الكرياتين للعضلات والدماغ (CK-MB)- كيناز الكرياتين للدماغ (CK-BB).

ومستويات اللاكتات بالمصل (Serum Lactate) هي مؤشرات بيوكيميائية حيوية مفيدة -وإذا تم إجراؤها بشكل روتيني في الساعات القليلة الأولى بعد الولادة لحديثي الولادة المشتبه باصابتهم بهذا الاعتلال الدماغي فان ذلك قد يؤدي إلى التشخيص المبكر والتدخل العلاجي في وقت مناسب- حتى قبل ظهور العلامات السريرية الكاملة لهذا الاعتلال الدماغي.