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*RESEARCH ARTICLE*

# EVALUATION OF BIOCHEMICAL AND OXIDATIVE STRESS MARKERS AS PREDICTIVE TOOL FOR DIAGNOSIS OF BIRTH ASPHYXIA AND ENCEPHALOPATHY IN NEW BORN

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## *Abstract*

**Background**:Birth asphyxia and resultanthypoxic ischemic encephalopathy (HIE), are leading cause of mortality and morbidity in newborns. Delayed diagnosis may lead to progression of HIE as its clinical features may not be evident at birth as they evolve with time. This study was done to identify asphyxia and HIE in term neonates by evaluating biochemical and oxidative stress markers in umbilical cord blood sample taken immediately after delivery.

**Methodology:** This prospective cross sectional study was done on term neonates in a tertiary care hospital (n=60)Thestudy population was then divided into two equal groups on the basis of Apgar score at 1 minute, with score < 7 as cases (n=30) and ≥7 as controls ( n=30) . The umbilical cord blood was evaluated for biochemical and oxidative stress markers like lactate dehydrogenase (LDH), creatine kinase brain isoform (CK BB), superoxide dismutase (SOD,malondialdehyde (MDH) and catalase.

**Result:** The mean values of LDH, CK BB, and MDA were higher in cases than controls and the differences were highly significant statistically. The mean values of SOD and catalase were higher in cases than controls and the differences were significant statistically. However, mean value of LDH & CKBB of cases with prolonged asphyxia with Apgar score < 7 at 5 minutes (n=4) versus cases with Apgar score > 7 (n=26) was not statistically significant at 95% CI.

**Conclusion:** This study helps in diagnosis of neonatal asphyxia at an early stage thereby preserving the normal functioning of neonatal brain so that the brain functioning is not compromised.



## Introduction:-

WHO has defined birth asphyxia (BA) also referred as perinatal asphyxia as a "failure to initiate and sustain breathing at birth".The term Hypoxic Ischemic Encephalopathy (HIE) has been used for the hypoxic ischemic injury to the central nervous system (CNS) and the resultant clinical manifestations due to perinatal asphyxia.[1] The incidence of HIE is estimated at 3 per 1,000 live births [2].

Birth asphyxia and resultant HIE is an important contributor to neonatal morbidity and mortality. More so in developing countries like India. It is estimated that 23% of all newborn deaths are caused by birth asphyxia.[3]

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Hypoxic-ischemic encephalopathy (HIE) is the most severe outcome of neonatal asphyxia and it is a syndrome characterized mainly by abnormal muscle tone and reflexes. These changes occur due to cerebral hypoxia, which a newborn may develop for a variety of reasons. HIE remains a common cause of death in newborns, and newborns who survive are prone to develop serious neurological disorders such as cerebral palsy. In countries with low neonatal mortality rates, 1.6/1,000 of these will develop hypoxic-ischaemic encephalopathy (HIE). On a global level, HIE causes nearly 1 million neonatal deaths each year.[4] Delayed diagnosis may lead to progression of HIE as it's clinical features may not be evident at birth as they evolve with time. So, this study was done to identify asphyxia and HIE in term neonates by biochemical (lactate dehydrogenase (LDH), creatine kinase brain isoform (CK-BB) and oxidative stress markers (superoxide dismutase(SOD), malondialdehyde (MDA) and catalase in umbilicalcord blood sample taken immediately after delivery.

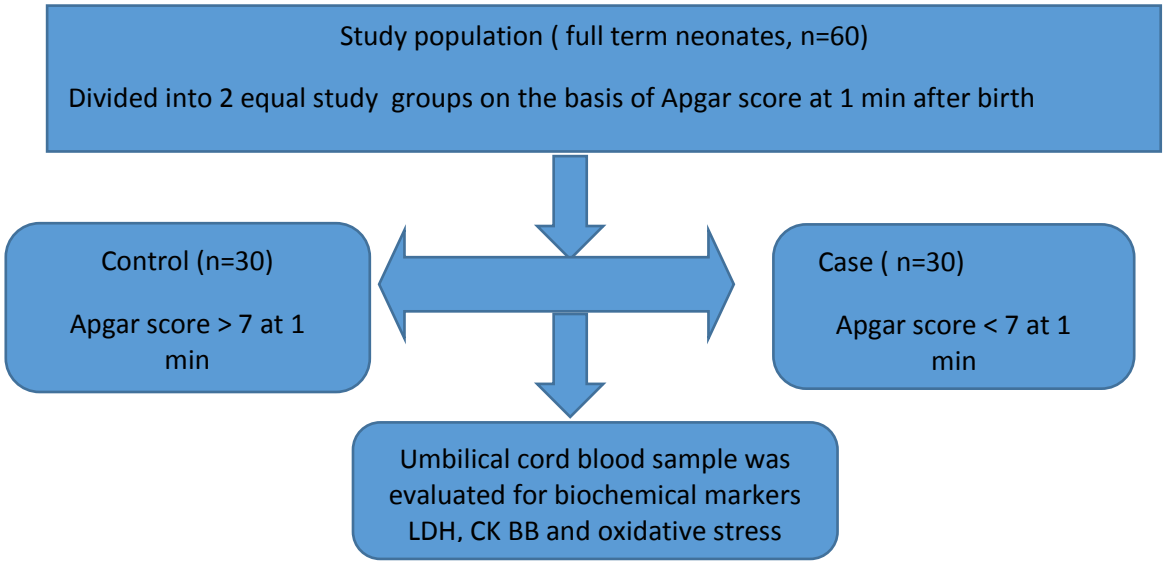
## Objectives:-

1.Primary objective was to determinethe efficacy of biochemical markers like LDH and CKBB and oxidative stress markers like like malondialdehyde, catalase and SOD to identify full term neonates at risk of birth asphyxia and HIE
2. Secondary objective was to identify full term neonates at risk of birth asphyxia to prevent or delay the onset of HIE.

## Material And Methods:-

Study design, participants and data collection

1. This prospective cross sectional analytical (case control )study was done on term neonates delivered in , a tertiary care hospital in North India (n=60) from May to December 2018. Sample collection was purposive
2. The sample size was calculated by the formula at 95 % Confidence Interval [5]
3. Sample Size= $(Z_{1-\alpha/2})^2 * p(1-p)/d^2$
4. The sample size calculated using this formula where $Z_{1-\alpha/2}$ was 1.96, p was 3 per thousand live births (based on previous studies) and d=5 percent(margin of error) was 45. 60 samples were taken in order to make two equal arms and having substantially higher sample size than minimum required.
5. Bias was taken care of by data analysis done by blinded person.
6. The study population was then divided into two equal groups on the basis of Apgar score at 1 minute, with score < 7 as cases (n=30) and ≥7 as controls (n=30). [6] .
7. Neonates delivered pre term, with congenital malformation, those born to mothers who had received magnesium sulphate within 4 hours before delivery or opioids (pharmacological depression), with haemolytic disease and severe infection were excluded from the study.The study was approved by the Jamia Hamdard Institutional Ethics Committee vide letter number nil dated 16/08/2018



**Study workflow**

The umbilical cord blood sample was collected under full aseptic measures after taking informed consent from parents of the cases and controls. The sample was then evaluated for biochemical markers like lactate dehydrogenase (LDH) [ 7], CK BB [8] and oxidative stress markers like MDH [9] catalase [10] and SOD [11]

Data was analyzed using SPSS version 26. Mean value and SD for different biochemical and oxidative stress markers were calculated using independent "t" test. "p " value for comparison of different markers between groups was calculated using independent "t" test.

## Results:-

This prospective cross sectional study was done on term neonates in a tertiary care hospital (n=60).The study population was then divided into two equal groups on the basis of Apgar score at 1 minute, with score < 7 as cases (n=30) and ≥7 as controls ( n=30) .Table 1 and graph 1 shows that the difference in mean value of LDH in control ([392.57 ±19.3] versus that of case [ 710.72 ± 34.85 , p value 0.0001] , CK BB in control [ 27.97 ± 2.8] versus case [ 42.13 ± 3.71, p value 0.0014] and MDA in control [ 1.64 ± 0.16 ] versus case [ 2.90 ± 0.22 , p value 0.0001] were statistically highly significant. The difference in mean value of catalase in control [ 49.36 ± 5.3] versus case [ 72.52 ± 7.9, p value 0.018] and SOD in control [ 12.43 ± 0.70] versus case [ 15.94 ± 1.23, p value 0.016] were statistically significant.

Table 2 and graph 2 shows the comparison in mean value of LDH and CKBB between group 1 of case (Apgar score < 6 at 5 min, n=4) and group 2 of case (Apgar score > 7 at 5 min, n=26 ) .The mean value of LDH in group 1 of case [ 839.0 ± 93] versus group 2 of case [ 689.72 ± 36.05, p value 0.42] and CKBB in group 1 of case [ 49.07 ±11.8] versus group 2 of case [ 41.07 ± 3.83 , p value 0.46] was statistically insignificant.

**Table 1:-** Comparison of mean value and SD of parameters in case versus control.

| | **LDH (IU/l) Mean** ± SD | **CKBB (ng/ml) Mean** ± SD | **MDA (µmol/l) Mean** ± SD | **CATALASE (KU) Mean** ± SD | **SOD (U/L) Mean** ± SD |
|---|---|---|---|---|---|
| **CONTROL (n=30)** | 392.57± 19.31 | 27.97± 2.8 | 1.64±0.16 | 49.36± 5.3 | 12.43± 0.70 |
| **CASE (n=30)** | 710.72±34.35 | 42.13±3.17 | 2.9±0.22 | 72.52±7.9 | 15.94 ±1.23 |
| **"p"value** | 0.0001 | 0.0014 | 0.0001 | 0.018 | 0.0161 |

**Figure 1**

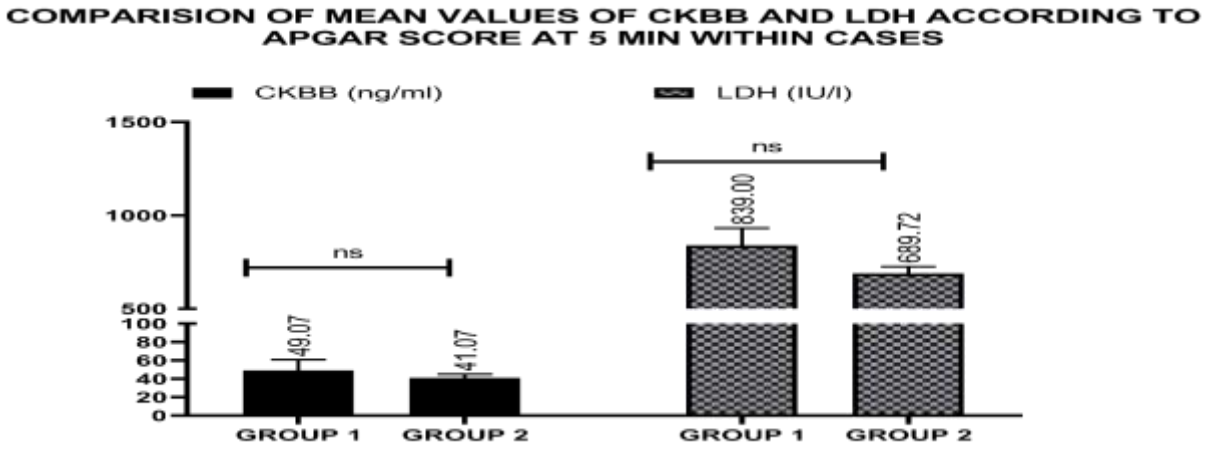
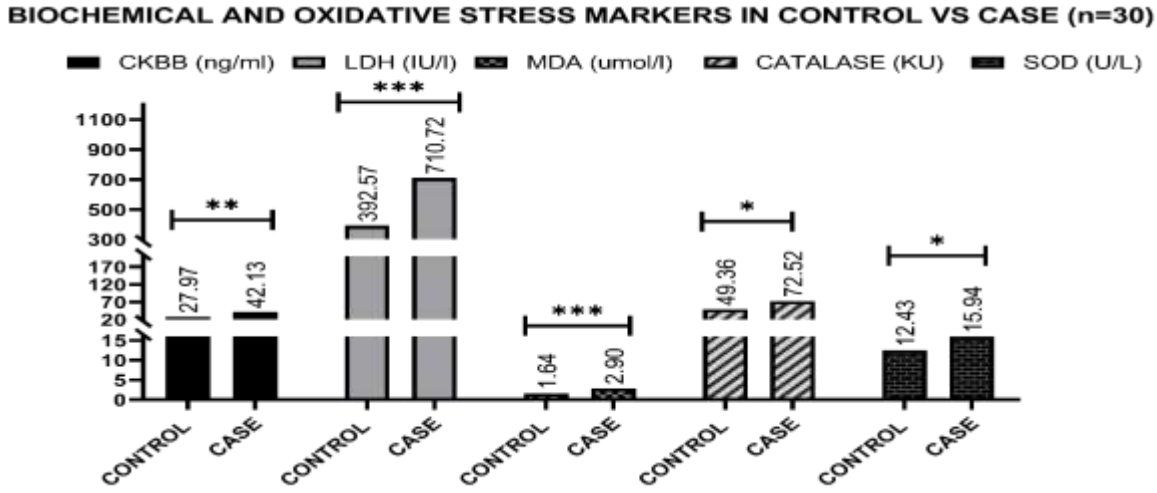


**Table 2:-** Comparison between 2 groups in cases on the basis of Apgar score at 5 min.

| CASE | CKBB (ng/ml) **Mean** ± SD | LDH (IU/l) **Mean** ± SD |
|---|---|---|
| **APGAR SCORE <6 AT 5 MIN (n=4) (GROUP 1)** | 49.07 ± 11.8 | 839±93 |
| **APGAR SCORE >7 AT 5 MIN (n=26) (GROUP 2)** | 41.07±3.83 | 689.72±36.05 |
| **p value** | 0.4843 | 0.1630 |

**Figure 2**




## Discussion:-

Birth asphyxia and resultant HIE is an important contributor to neonatal morbidity and mortality. More so in developing countries like India,it is estimated that 23% of all newborn deaths are caused by birth asphyxia. [3] Hypoxic-ischemic encephalopathy (HIE) is a common disease caused by neonatal asphyxia, a major cause of neonatal death, neurological behavior, and long-term disability.[12]

In the present study the mean value of LDH was statistically highly significant in cases versus control (p value=0.000). The finding is in line with the study by Ton NV Anh and Tran K Hao where they have concluded that plasma LDH level can be a good marker for the prognosis of severe conditions in newborn infants, including early-onset neonatal sepsis, asphyxia, and respiratory-distress.[13] In asphyxia as the oxygen concentration is deficient, glucose is metabolized by the anaerobic pathway, and pyruvate is then converted into lactate by lactate dehydrogenase. As the oxygen deficiency is compensated by increase in the rate of anaerobic metabolism a simultaneous increase in levels of the LDH is seen leading to increase in concentration of lactate[13]. Enzyme leakage as a result of hypoxia-ischaemia induced cell damage in affected organs is seen together with hypoxic ischaemic encephalopathy (HIE) after perinatal asphyxia.[14] The study is also in line with the finding of study by where they have shown that leakage of intracellular enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) signalling multiorgan dysfunction (MOD) is seen together with hypoxic ischemic encephalopathy (HIE) after perinatal asphyxia, thereby explaining their role as potential predictors of timing and grade of the hypoxic ischemic injury in both the perinatal period and in infants with antepartum asphyxia [15]. LDH, being intracellular, may readily increase whenever there is hypoxic ischaemic tissue damage and it is present in all tissues. LDH can be an ideal biomarker in birth asphyxia reflecting the severity of the cellular damage.[16] Even within the cases (n=30), the mean value of LDH in cases with HIE (n=4) was (839 ±93 IU/L) which was higher in comparison to the level in cases without HIE (n=26) (689.72 ± 36.05 IU/L). Though this difference is not significant statistically ,it tentatively indicates a a correlation between LDH & HIE suggesting that LDH can act as a biochemical marker of HIE along with asphyxia.

This finding is in line with the study byElsadek A, Barseem N and Abdelghani W where they had concluded that there was a significant positive correlation between LDH versus the HIE stage. [17]. This finding is also in line with the study by Itzel E, Hampus Josephson H, Wiberg N,Olson L,Winbladh B and Karlsson M where they had concluded that in newborns subjected to fetal distress and/or asphyxia, plasma LDH in the first hours of lifeseemed so far to be the best chemical predictor of newborns subjected to fetal distress and/or asphyxia, plasma LDH in the first hours of life seems so far to be the best chemical predictor of HIE [18]

In our study the mean value of CKBB {brain-specific creatine kinase (E.C. 2.7.3.2)} was highly significantly statistically in cases versus control (p value =0.0014)

This finding is in line with the study done by Nagdyman N, Kömen W, Ko HK, Müller C and Obladen M, where they have concluded that that elevated serum concentrations of CK-BB reliably indicates moderate and severe HIE as early as 2 h after birth. [19]. The increase in level of CKBB originated mainly from the brain of the asphyxiated infants and might be a simple epiphenomenon of general ischemia related to asphyxia. Asphyxia may involve the whole body, and the release of proteins into the blood might be a general sign of change in cell membrane integrity and vascular permeability caused by the whole body ischemic-reperfusion injury. The study is also supported by a similar finding in the study by Hesham Ibrahim E and Alaa Hwhere they have concluded that serum markers of brain injury as CK BB is predictive of HIE in full term neonates when measured soon after birth. [20]HIE is associated with increased risk of neonatal mortality; 15–20% of neonates die due to complications of perinatal asphyxia.HIE is a brain injury that prevents adequate blood flow to the infant's brain occurring as a result of a hypoxic-ischemic event during the prenatal, intrapartum or postnatal period. By the age of 2 years, up to 60% of infants with HIE die or have severe disabilities including mental retardation, epilepsy, and cerebral palsy[21] Mild encephalopathy carries a good prognosis, although in moderate and severe encephalopathy the risk of death or neurologic sequelae increases greatly. HIE must be identified as soon after birth as possible so that appropriate measures could be taken. Moreover, HIE often leads to sustained severe and irreversible brain damage.

Among 30 full term neonates with asphyxia (cases), four suffered from HIE as evident from their Apgar score at 5 min after birth which was less than 6 along with other neurological and electro-encephalogram (EEG) features in comparison to the rest 26 neonates who had not developed HIE. Among the 4 cases,1 was suffering from grade III HIE, 1 from grade I and 2 from grade I as per the grading by Sarnat & Sarnat. [22]. Among cases (n=30), the mean value of CKBB in cases with HIE (n=4) was 49.07 ± 11.8 ng/ml which was higher than that in cases without HIE (n=26) 41.07 ± 3.83 ng/ml. Though the difference was not significant statistically, it definitely points towards a correlation between CKBB and the severity of HIE.Our study is in line with the study by Nagdyman N, Kömen W, Ko HK, Müller C and Obladen M where they had concluded that serum CK-BB was significantly higher in infants with moderate or severe HIE when compared with infants with no or mild HIE 2, 6, and 12 h after birth.[19]

In the present study the mean value of MDA was statistically highly significant in cases versus control (p value =0.001) which is in line with the study by Seif El Dein, H.M., Fahmy, N., El Din, Z.E. *et al*and study by Manoj A, Rao R, Bhat V, Venkatesh C and Bobby Z. where they had concluded that serum MDA level was significantly more in asphyxiated babies than controls and correlated with severity of asphyxia.[23,24] Oxygen deprivation and excess accumulation of CO2 results in metabolic acidosis. alter the ionic exchange and cause defect in the liberation of ATP eventually leading to energy failure.The reduction of O2 results in the generation of reactive oxygen species Serum malondialdehyde is the end product of lipid peroxidation and a useful marker for the evaluation of oxidative stress .So it can therefore, be used as a predictor for determining the presence and severity of HIE.[23,24].

In the present study the mean value of catalase (E.C. 1.11.1.6) and superoxide dismutase (SOD) were statistically significant n cases versus control.( p value of catalase= 0.018 and of SOD = 0.016) This study is in line with the finding of Kumar A, Ramakrishna SV, Basu S, Rao GR [25] as well as Singh SK, Dua T, Tandon A, Kumari S, Ray G, Batra S [26]who have concluded that serum levels of catalase & SOD were significantly higher in newborns with perinatal asphyxia and demonstrated a progressive increase with greater severity of HIE. Free radicals are generated during stepwise reduction of molecular oxygen and are highly damaging. They pose serious threat to vital organs, tissues, polyunsaturated fatty acids (PUFAs) of cell membranes and nucleic acids of cells. PUFAs are most susceptible to injury and this self perpetuating destruction of PUFAs is known as lipid peroxidation. Superoxide dismutase (SOD), gluatathione peroxidase (GPx) and catalase are three important antioxidant enzymes which are found in all aerobic and aerotolerant anaerobic organisms protecting biological structures from free radical mediated

injury.[26]. Free radical injury involves the cooperative action of three main intracellular antioxidant enzymes: superoxide dismutase, glutathione peroxidase and catalase.

The increase in level of SOD & catalase may be due to production of $.0_2^-$ and $H_20_2$ in HIE cases and subsequent upregulation of antioxidant enzymes SOD and catalase

**Limitation**:
The sample size was small and only single umbilical cord blood sample was assessed. The study needs validation by a larger sample size and serial sampling at frequent intervals would have added more to this study.

**Generalisability**
The results of this study can be generalised as the asphyxiate neonates have same pathophysiology everywhere.

## Conclusion:-

The biochemical markers CKBB, LDH MDA, SOD and catalase help in identification of neonatal asphyxia as their levels were increased significantly in asphyxiated neonates as compared to non asphyxiated neonates

The biochemical markers CKBB, LDH, MDA, SOD and catalase help in identification of neonatal asphyxia as their levels were increased significantly in asphyxiated neonates as compared to non asphyxiated neonates. The thedifference in values of CKBB & LDH in asphyxiated neonates with HIE (n=4) in comparison to those in asphyxiated neonates without HIE (n=26), was not significant statisticallyThe key finding of the study is that the treating clinician can be made aware of the risk of neonate developing HIE. These biochemical markers can alert the clinician within 4 hours after birth so that the timely neuroprotective treatment protocols like controlled hypothermia treatment and phenobarbitone can be used which is likely to improve the outcome. These biochemical markers can be done in every hospital and do not need sophisticated instruments like ultrasonogram & electroencephalogram.The result can be more conclusive with a larger sample size and multicentric study .

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Nil.

**Conflict of interest**:
None.

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