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Original Research Article

A STUDY OF HEPATIC ENZYMES IN TERM AND PRE TERM NEWBORNS WITH BIRTH ASPHYXIA

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ABSTRACT

Background: Asphyxia is the commonest primary cause of neonatal death (54.9%). A biochemical parameter that correlates with hypoxic ischemic encephalopathy is of interest since ventilator treatment, sedative drugs and anticonvulsant therapy could make evaluation of severity of hypoxic ischemic encephalopathy difficult. **Objective:** To know the occurrence of hepatitis in full-term & preterm neonates after birth asphyxia and to know whether the degree of hepatitis due to asphyxia correlates with the severity of the asphyxia and CNS symptomatology. **Materials and Methods:** It is an Hospital based prospective study with sample of 50 term neonates & 50 preterm neonates with perinatal asphyxia, with 50 controls, admitted in Nicu in BTGH, STGH, Gulbarga. Informed written consent taken from parents relevant information from history was written in proforma Maternal, natal risk factors were noted. Apgar scores were documented. Cases were classified according to the stage. Blood sample is collected at 24 hours and at 72 hours after the birth for estimation of (SGOT), (SGPT) and (LDH). **Result:** Majority of mothers of neonates with birth asphyxia were primigravida (66%). PIH (28 %) was the most common risk factor in mothers of neonate with birth asphyxia. The mean Apgar score was significantly less in HIE Cases. The mean values of SGOT, SGPT, LDH in cases are significantly elevated than the control groups on both day 1 & day 3. The mean values of SGOT, SGPT are more on day 1, LDH is more on day 3 in term cases & preterm cases. The mean values of SGPT, LDH are higher in term cases than the preterm groups. Of the total 100 neonates, HIE III had 43.7% mortality as compared to 10.4 % in HIE II group and one deaths in HIE I with a significant p value of < 0.001. All the mean enzymes levels i.e. LDH, AST, ALT studied on day I and 3 of life show higher values in non survivors than the survivors in both term & preterm asphyxiated group & the elevation is significant in LDH. **Conclusion:** liver enzymes can be used as prognostic indicator for aid in counselling in relation to newborns with HIE. The tests are affordable, feasible, acceptable, so they can be used as bed side test for predicting outcome.

INTRODUCTION

Birth Asphyxia is the commonest primary cause of neonatal death (28.8%). In India, 8.4% of inborn babies have a 1 minute Apgar score less than 7 and 1.4% suffer from hypoxic ischemic encephalopathy (HIE).[1]

Birth asphyxia is an eventuality having far-reaching effects in the neonatal period. The asphyxia attack leading to hypoxic ischemic encephalopathy (HIE) could start either at the antenatal or perinatal period.[2]

Perinatal hypoxia is considered when a neonate demonstrates all of the following:

Profound metabolic or mixed acidemia (pH ,7.00) on an umbilical arterial blood Sample, if obtained;

An Apgar score of 0–3 for longer than five minutes. Neurologic manifestation, example, seizure, coma, or hypotonia and Evidence of multi organ dysfunction.3 The other criteria that can define asphyxia and HIE included

- Prolonged (1 hour) antenatal acidosis.
- Foetal heart rate less than 60 bpm.
- Apgar score <3 at 10 minutes
- Need for positive pressure ventilation for.1 minute or first cry delayed for. 5 minutes.
- Seizures within 12–24 hours of birth, and
- Burst suppression or suppressed background pattern on electroencephalography (EEG) or amplitude integrated electroencephalography (aEEG).[4]

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Apgar scoring is used as a predictor of survival in asphyxiated neonates, but it can also be decreased in depression from maternal drugs, anomalous babies, trauma, metabolic, & other insults.

The predictive value of Apgar score for detection of hypoxic ischemic encephalopathy is insufficient during first hour of life.[5]

A biochemical parameter that correlates with hypoxic ischemic encephalopathy is of interest since ventilator treatment, sedative drugs and anticonvulsant therapy could make evaluation clinically difficult. Injured cells leak intracellular enzymes like lactate dehydrogenase, glutamic oxaloacetic transaminase, glutamic pyruvate transaminase. These enzymes may be used as potential predictors of timing and grade of hypoxic ischemic injury in both perinatal period and in infants with antepartum asphyxia.[5,6]

MATERIALS AND METHODS

This hospital based prospective study was conducted among 50 consecutive term neonates with perinatal asphyxia & 50 preterm neonates with perinatal asphyxia, with 50 controls, admitted in NICU in Basaveshwar Teaching & General Hospital and Sangameshwar Hospital, kalaburagi attached to M.R. Medical College, Gulbarga.

Inclusion Criteria

- Full term neonates [gestational age between 37 to 42 weeks].
- Pre term neonates [gestational age 37 weeks]
- Resuscitation with more than 1 min of positive ventilation before stable spontaneous
- respiration
- Apgar score less than 7 at 5 minutes of birth
- Neonatal neurological sequel
- Multiple organ involvement

Exclusion Criteria

- Neonates with congenital anomalies.
- Neonates with cardiac, renal, other anomalies.
- Neonates born to mothers with viral hepatitis.
- A predesigned, pre structured proforma will be used for collection of neonatal and maternal data.
- Pretest and posttest counselling is given to parents / guardian.

Method of collection of data

Blood sample is collected at 24 hours after birth and at 72 hours after the birth for estimation of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT) and serum lactate dehydrogenase (LDH) after taking informed written consent from parents.

Reference ranges for enzymes

SGOT, (AST) > 140 U/L

SGPT, (ALT) > 50 U/L

LDH > 580 U/L

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. The Statistical software namely SPSS 21.0, Med Calc 17.9.7 and were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Results on continuous, measurements are presented on Mean ± SD (Mm-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters, Chi square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

Total male cases are 30, female cases are 20 among term asphyxiated newborns. Male cases are more than Female cases, HIE cases are 37 among 50.

Of total term cases , HIE is present in 37 cases, of which stage 1 present in 13 cases, 17 in stage 2, 7 in stage 3 .Males are more than female cases, number of HIE cases are 31 among 50. Of preterm cases, 32 cases are with HIE, among them stage 1 is present in 10 cases, stage 2 in 13 cases, 9 in stage 3.

Most of the cases are above 2.5 kg birth weight.

In term cases males are 33, & females are 17 in number.

In preterm cases males are 26 females are 24 in number.

There is no significant difference in gender distribution between term & preterm cases

Table 1: Mean APGAR scores in term cases

HIE		N	Mean	Std. Deviation
Absent	apgar-1min	13	4.54	1.050
	apgar-5min	13	5.38	1.044
Present	apgar-1min	37	3.19	1.151
	apgar-5min	37	4.73	.902

Mean Apgar scores are less in cases with HIE than in cases without HIE at 1 & 5 Min

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Table 2: Mean APGAR Scores in Preterm Cases

HIE		N	Mean	Std. Deviation
Absent	apgar-1min	19	3.89	1.049
	apgar-5min	19	5.84	.375
Present	apgar-1min	31	2.84	.969
	apgar-5min	31	5.10	.908

Mean Apgar scores are less in cases with HIE than in cases without HIE at 1 & 5 Min.

Parity distribution showed majority of cases mothers are primi than multiparous. Normal vaginal delivery is seen more in term cases than preterm cases.

In antenatal risk factors studied PIH is seen more in preterm cases. There is no much difference in APH risk factor in term cases & preterm cases. MSAF is seen more common in term neonates than preterm neonates.

In term cases with birth asphyxia the mean levels of SGOT, SGPT are more on day one, & the mean levels of LDH are more on day three.

Similar to term cases in pre term cases with birth asphyxia the mean levels of SGOT, SGPT are more on day one & LDH levels are more on day three.

Table 3: Comparison of SGOT, SGPT, LDH in Term Cases Vs Controls

Group Statistics							
TERM		**case/control**	**N**	**Mean**	**Std. Deviation**	**t**	**P Value**
TERM	**SGOT-DAY1**	**CASE**	50	119.24	64.798	4.406	0.0001
		CONTROL	25	57.56	36.912		
	SGOT-DAY3	**CASE**	50	89.40	91.851	2.502	0.015
		CONTROL	25	41.96	31.647		
	SGPT-DAY1	**CASE**	50	78.46	50.702	5.198	0.0001
		CONTROL	25	25.24	8.146		
	SGPT-DAY3	**CASE**	50	66.74	49.176	4.290	0.0001
		CONTROL	25	24.20	6.868		
	LDH-DAY1	**CASE**	50	783.58	316.862	6.498	0.0001
		CONTROL	25	357.44	114.301		
	LDH-DAY3	**CASE**	50	967.52	510.713	5.491	0.0001
		CONTROL	25	397.00	121.099		

On day 1, & day 3, SGOT, SGPT, LDH mean levels are more in term birth asphyxia cases than controls and the values are significantly elevated

Table 4: Dynamics of SGOT in Term Birth Asphyxia Cases According to HIE Stage On day 1

One-Sample t test						
HIE stage		**N**	**Mean**	**Std. Deviation**	**t**	**P**
0	**SGOT-DAY1**	13	96.92	61.679	5.666	0.0001
1	**SGOT-DAY1**	13	119.31	50.968	8.440	0.0001
2	**SGOT-DAY1**	17	128.82	62.314	8.524	0.0001
3	**SGOT-DAY1**	7	137.29	97.017	3.744	0.010

Table 5: Dynamics of SGOT in Term Birth Asphyxia Cases According to HIE Stage On day 3

One-Sample Statistics						
HIE stage		**N**	**Mean**	**Std. Deviation**	**t**	**P**
0	**SGOT-DAY3**	13	60.38	74.104	2.938	0.012
1	**SGOT-DAY3**	13	64.38	50.054	4.638	0.001
2	**SGOT-DAY3**	17	102.53	114.338	4.418	0.001
3	**SGOT-DAY3**	7	119.29	106.263	2.721	0.035

The mean value of SGOT is increased as the HIE stage is progressed from zero to three which is statistically significant.

Table 6: Dynamics of SGPT in Term Birth Asphyxia Cases According to HIE Stage On day 3

One-Sample Statistics						
HIE stage		**N**	**Mean**	**Std. Deviation**	**t**	**P**
0	**SGPT-DAY3**	13	48.15	37.813	4.592	0.001
1	**SGPT-DAY3**	13	88.85	59.998	5.339	0.0001
2	**SGPT-DAY3**	17	61.06	41.621	6.049	0.0001
3	**SGPT-DAY3**	7	74	55.77	3.511	0.013

One-Sample t test used

The mean value of SGPT is increased as the HIE stage is progressed from zero to three which is statistically significant.

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Table 7: Comparison of SGOT, SGPT, LDH IN Pre Term Cases Vs Controls

One-Sample Statistics						
HIE stage		N	Mean	Std. Deviation	t	P
0	LDH-DAY3	13	560.62	153.489	13.169	0.0001
1	LDH-DAY3	13	781.69	224.068	12.578	0.0001
2	LDH-DAY3	17	1000.47	294.058	14.028	0.0001
3	LDH-DAY3	7	1988.29	315.778	16.659	0.0001

The mean value of LDH is increased as the HIE stage is progressed from zero to three which is statistically significant.

On day 1, & day 3, SGOT, SGPT, LDH mean levels are more in Preterm birth asphyxia cases than controls and the values are significantly elevated.

The mean value of SGOT, SGPT, LDH is increased as the HIE stage is progressed from zero to three which is statistically significant.

Out of total 50 term cases studied, six cases died. The mean values of liver enzymes i.e. SGOT, SGPT, LDH are elevated in term survivor group compared to non survivors on day one & day three and the values are significantly elevated on Day 1 & day 3 LDH.

Out of total 50 preterm cases studied, five cases died. The mean values of liver enzymes i.e. SGOT, SGPT, LDH are elevated in term survivor group than in non survivors on day one & day three and the values are significantly elevated in Day 3 LDH.

Ultrasound cranium was done in the cases. Out of 50 term cases eleven cases had abnormality in the ultrasound cranium. Most common abnormality detected is altered parenchymal echogenicity, cerebral oedema which in seven cases. Four cases had intra parenchymal bleed. Out of 50 preterm cases thirteen had ultrasound abnormality. Most common abnormality detected is periventricular leucomalacia Which is seen in eight cases. Five cases had periventricular bleed. Two cases had absent choroid plexus. Four cases had hydrocephalus.

DISCUSSION

The prognostic value of the Apgar score for detection of hypoxic ischemic brain disease is insufficient during the first hour of animation because it can be decreased during depres¬sion from maternal drugs, anomalous babies, trauma, or metabolic or infectious insults. A biochemical parameter that correlates with HIE is of interest since ventilator treatment, sedative drugs, and anticonvulsant therapy could bring on an evaluation of severity of HIE difficult.

Perinatal asphyxia is a major problem in the care of high risk neonates. Despite increasing knowledge about the pathogenesis of these asphyxia related disorders, it often remains difficult to predict which newborn will develop clinically relevant neurologic problems.

Beyond perinatal hypoxic ischemic events & the prematurity itself as major risk factors, newborns with severe acidosis, low birth weight, low Apgar scores, and those delivered vaginally have been considered at risk for the development of HIE

Multiple organ dysfunction in birth asphyxia is a possible issue of adaptive mechanism. Thus, if the contrary effects of hypoxia on the newborns are considered, there is a demand to identify infants who will be at high risk of hypoxic ischemic brain disease and early neonatal death as a result of perinatal hypoxia.

Different kinds of markers have been studied to iden¬tify perinatal hypoxia, including electronic fetal heart moni¬toring, cord pH, electroencephalograms, and Doppler flow studies. Supplementary methods for diagnosis and prediction of antenatal and non-acidotic prolonged asphyxia are lacking. Injured cells leak intracellular enzymes such as LDH, alanine transaminase, and aspartate transaminase.

These enzymes may be utilized as possible predictors of timing and grade of hypoxic ischemic injury in both perinatal period and in infants with antepartum asphyxia. To know whether hepatic dysfunction can be employed as a prognostic tool for assess¬ment of the level of hypoxia ischemic brain disease during the beginning hours of life, the study was undertaken.

In this study, hepatic involvement in term neonates with HIE studied was 82% which comparison is similar to studies done by Shah et al,[7] and Md tariqul islam et al,[8] which showed 84.6 % and 87.1 % respectively.

In the present study, the incidence of elevated LDH was significantly more in neonates with HIE on both day 1 and 3 in comparison to the control group with a p value of <0.001.

Deepthi ramu et al,[9] in their study found a similar significant difference between the two groups of neonates studied with a p value of <0.01,

Sanath Reddy et al,[10] in their study done at PGI, India had studied a single value at 72 hours of life had a significant p value of <0.001 with similar results as in present study.

The LDH levels on day 3 were significantly elevated with in the groups & it is statistically significant.

Similar results were obtained in a study conducted by Mukesh Choudhary, et al.[11]

The results of the mukesh chowdary et al On day 3, LDH was 1205.42 ± 655.55 U/L in group A as compared to 322.33 ± 122.02 U/L in group B, which was significant (P = 0.001). There was a rising trend observed in the concentration of mean LDH as HIE staging of neonates progressed from HIE stage 0 to HIE stage III on day 3. Among various HIE stages, the difference in LDH was statistically significant between HIE 0–II (P= 0.001), HIE 0–III (P = 0.001), HIE I–II (P, 0.001), and HIE I–III (P, 0.001).

A serial rise in levels of LDH or failure to come down in the beginning few days of life indicates hepatic

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impairment. LDH levels increased in response to asphyxia insult.

We observed significantly higher LDH in asphyxiated babies, and similarly, Lackmann and Töllner,[12] (8) Karlsson et al,[13] reported higher mean LDH in asphyxiated neonates. In the current work, peak LDH levels were on day 3, and among various HIE stages, the difference in LDH was statistically significant.

In the present study, the mean AST values were statistically significant between the cases and the controls with a p value of <0.001.

In studies done by Sanath Reddy et aL,[10] and Md Tariqul Islam et al,[8] there was similar statistically significant difference between cases and control neonates studied on day 3 of life, but all the three studies had lower mean value in comparison to the present study probably due to different methods used for enzyme assay.

In the present study, the mean ALT values were statistically significant between the cases and the controls with a p value of <0.001. Karisson et al,[13] in their study found a similar significant difference between the two groups of neonates studied with a p value of 0.002 with mean values being higher in the cases as in this study there are more number of neonates with HIE III i e 41% of total, in comparison to the present study which was 14 % of total and also studies done at two different places, with inter lab variation.

In studies by Md Tariqul Islam et al8 and Saili et al, there was a statistically significant difference between mean values in cases and controls groups, but in a study done by Sanath Reddy et al,[10] there was no significant difference in the mean values between two groups possibly due to a small sample size of 25 neonates with HIE studied.

Hepatic dysfunction observed in the study is 68%. The study conducted by Gerd M Lackmann et al,[12] showed similar findings.

In the present study SGOT levels in the preterm groups are elevated both at 24 hours & 72 hr. and the elevation is statistically significant.

Similar to that Gerd M Lackmann et al,[12] conducted a study in 50 preterm newborns with
asphyxia the sgot levels are significantly more in comparison to controls at day 1 & day 3.

But the study conducted by Zanardo V, Bondio M et al,[14] levels at day 3 were not statistically more in comparison to controls.

The study also demonstrates there is elevation in SGOT in comparison to various HIE stages and the elevation is statistically significant.

Similar study was also done by Gerd M Lackmann et al,[12] which also showed similar results.

The higher the stage of HIE the higher the elevation in SGOT enzyme.

On day one, & day three, SGOT, SGPT, LDH mean levels are more in Preterm birth asphyxia cases than controls and the values are significantly elevated.

Similar findings are observed in a study conducted by Gerd M Lackmann,[12] where the study was conducted in SGOT, LDH levels.

The present study shows that there is elevation in LDH levels in preterm asphyxiated newborns on day one & day 3 and elevation is statistically significant. Similar findings are observed in a study conducted by Gerd M Lackmann.[12]

In the present study there was significant elevation in mean values in HIE III as compared to HIE I and II. Similar findings are observed in a study conducted by Gerd M Lackmann.[12]

In our study the mean values of SGPT, are higher in term cases than the preterm groups on both day one and day three, with a significance noted on day one. In contrast to our Similar findings are noted in a study done by Zanardo V, Bondio M et al.[14]

CONCLUSION

The mean Apgar score was significantly less in HIE Cases than cases with birth asphyxia Without HIE, PIH was the most common risk factor in mothers of neonate with HIE In Term & Preterm cases. The mean values of SGOT, SGPT, LDH in cases are significantly elevated than the control groups on both day 1 & day 3 and the difference is statistically significant. The mean values of SGOT, SGPT are more on day one and the mean value of LDH is more on day three in term cases. Similar findings are seen in preterm cases. There was significant difference between the mean enzyme values of LDH, AST, ALT in all the three stages of HIE with stage III having a higher mean value as compared to II and I, both in term newborns & preterm newborns. All the mean enzymes levels i.e. LDH, AST, ALT studied on day I and 3 of life show higher values in non survivors than the survivors in both term asphyxiated group & preterm asphyxiated group & the elevation is statistically significant in LDH. This study shows significance of doing liver enzymes on day one & day three for prognostication of asphyxiated newborns.

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