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Hepatic Enzyme Study In Term And Preterm Newborns With Birth Asphyxia: A Hospital-Based Study

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Abstract

Introduction: Perinatal asphyxia, a critical global health concern, contributes to significant neonatal morbidity and mortality. Hypoxic hepatic injury (HHI), characterized by elevated hepatic enzymes, is a potential consequence. This study explores the prevalence and implications of hepatitis in newborns with birth asphyxia, focusing on aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) levels.

Methodology: Conducted at SCB Medical College and Hospital, Odisha, from December 2020 to November 2022, the study enrolled 200 newborns (100 perinatal asphyxia cases, 100 controls). Gestational age, birth weight, and gender were matched. Serum samples were collected on days 1 and 3, with statistical analysis using IBM SPSS.

Results: 68% of asphyxiated newborns showed HIE. ALT, AST, and ALP levels were significantly higher in asphyxiated infants compared to controls ($p<0.001$). Day 3 ALP showed a significant increase. ALT demonstrated high sensitivity (95.7%) and specificity (88.46%) at a cutoff of 56.3 U/L.

Discussion: The study contributes nuanced insights into hepatic enzyme dynamics, emphasizing their potential as early markers of HHI. Consistent findings with existing literature validate the robustness of results. ALT, AST, and ALP levels correlated with HIE severity, highlighting their potential as markers.

Conclusion: Birth asphyxia poses a substantial risk of hepatitis, impacting 68% of affected newborns. Elevated ALT, AST, and ALP levels provide valuable diagnostic and prognostic information. ALT, particularly, emerges as a potent diagnostic marker, potentially reshaping early identification and intervention strategies in perinatal asphyxia. Further research is warranted to explore comprehensive liver function tests and establish direct links between hepatic complications and clinical outcomes.

Keywords: Hospital Based, Asphyxia, Newborn, Liver, Hepatic enzyme.

INTRODUCTION

Perinatal asphyxia, defined by the World Health Organization (WHO) as the failure to initiate and sustain breathing at birth, poses a significant global health concern. Even when not fatal, it represents a precarious

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metabolic challenge with potential long-term complications[1]. Approximately 23% of neonatal deaths worldwide are attributed to perinatal asphyxia, making it one of the top three causes[2]. The global incidence ranges from 1 to 6 per 1000 live full-term births, affecting between four and nine million newborns annually. This results in an estimated 1.2 million deaths and a similar number of cases with severe, enduring complications[3-4].

Clinical diagnosis of birth asphyxia relies on the Apgar score, an objective tool assessing physiological adaptation based on five parameters: heart rate, respiratory effort, muscle tone, reflex irritability, and colour[5]. The 5-minute Apgar score is a more reliable predictor of mortality and significant brain damage compared to the 1-minute score[6]. According to WHO's ICD10 classification, an Apgar score of 0–3 at 1 minute defines severe birth asphyxia, while a score of 4–7 indicates mild to moderate asphyxia[6-8]. The hypoxic-ischemic insult during birth triggers protective reflexes, known as diving sea reflexes, prioritizing blood flow to vital organs such as the brain, heart, and adrenals over less vital organs like the kidney, lungs, gastrointestinal tract, liver, and spleen[9-11].

Hypoxic hepatic injury (HHI) refers to hepatocyte damage resulting from birth asphyxia, characterized by a sudden surge in aspartate transaminase (AST) and alanine transaminase (ALT) levels within 24–72 hours of the insult, returning to normal within 7–10 days[12-14]. The neonatal hepatocellular cell membrane's higher permeability and increased biosynthetic activity, along with factors like skeletal muscle trauma and erythrocyte breakdown, contribute to elevated transaminase levels in non-asphyxiated neonates[12-13].

Some studies indicate a correlation between elevated hepatic enzymes and the severity of hypoxic ischemic encephalopathy (HIE). Full-term asphyxiated neonates with HIE show significantly elevated AST, ALT, and lactate dehydrogenase levels at birth and within the first 24 hours. Even without HIE, asphyxiated neonates exhibit elevated enzymatic activity, albeit at lower levels. The elevation in enzyme levels is more pronounced in cases of severe HIE, establishing a potential correlation between AST and ALT levels and the severity of birth asphyxia1[14-15].

Aspartate transaminases (AST) and alanine transaminases (ALT) signify hepatocellular injury, while bilirubin and alkaline phosphatase indicate hepato-biliary dysfunction and cholestasis[16-17]. Severe neonatal asphyxia may lead to cholestasis, with about 10% of cases showing elevated ALP[18].

In the context of perinatal asphyxia, where clinical evaluation can be challenging due to ventilator treatment and other therapies, exploring biochemical parameters becomes crucial. Intracellular enzymes like lactate dehydrogenase, glutamic oxaloacetic transaminase, and glutamic pyruvate transaminase, released from injured cells, hold promise as potential predictors of timing and grade of hypoxic ischemic injury during the perinatal period and in infants with antepartum asphyxia.

Despite limited research on liver dysfunction in term neonates with birth asphyxia in India, this case–control study aims to compare the severity of liver dysfunction in term and preterm neonates with perinatal asphyxia to those without perinatal asphyxia.

Aims and objectives-

1. To determine the incidence of hepatitis in full-term and preterm neonates following birth asphyxia.
2. To establish a correlation between the degree of hepatitis due to birth asphyxia and the severity of asphyxia and central nervous system (CNS) symptomatology.
3. To evaluate whether elevated enzyme levels can serve as prognostic indicators for assessing the degree of hypoxic-ischemic encephalopathy within the first few hours of life and aid in counseling.

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METHODOLOGY

This study was carried out at the SCB Medical college and Hospital in Odisha from December 2020 to November 2022. We enrolled the newborns after the parents gave consent for their newborns to be part of the study.

Inclusion criteria: Full-term neonates (Gestational age 37 to 42 weeks) and Preterm neonates (Gestational age <37 weeks) with , Resuscitation at Birth before establishment of stable spontaneous respiration and Neonatal neurological sequel as determined by Levene classification of HIE.

Exclusion criteria: Patients who did not meet the criteria of perinatal asphyxia, Neonatal with congenital anomalies, Neonatal Sepsis and Neonates born to mothers with viral hepatitis.
We collected data using a special form about mothers, newborns, and any risks they had. We used a scoring system called LEVENE to group the cases.

To understand more about the newborn' health, we took blood samples at 24 hours and 72 hours after birth. We checked for substances in the blood related to the liver using machines that measured light at specific colors. To compare, we also collected blood from 50-term and 50 preterm babies without birth problems. We then used a statistics package IBM SPSS to analyze the data. We calculated percentages, averages, and other differences. In the end, we used ROC to see how well the liver tests could tell us about the newborn's health.

RESULT –

Of the 200 babies studied (100 with perinatal asphyxia and 100 controls), both groups were matched for gestational age. The mean gestational age was 36±2.84 weeks, and the mean birth weight was 2.47 ± 0.537 kg. Among the newborns, 54% were male, and 77% were Appropriate for Gestational Age (AGA). Out of the 100 asphyxiated newborns, 68% had Hypoxic-Ischemic Encephalopathy (HIE), with Grade 2 being the most common.

Table 1 Distribution Of Study Participants

		FREQUENCY (n)	PERCENTAGE (%)
WEIGHT FOR AGE	SGA	44	22
	AGA	154	77
	LGA	2	1
STATUS OF HIE	Non HIE	32	32
	HIE1	20	20
	HIE2	36	36
	HIE3	12	12

The mean ALT levels for all 200 newborns were 53.4 ± 28.2 U/L on Day 1 and 55.4± 29.2 U/L on Day 3. The mean AST levels were 67.5 ± 31.2 U/L on Day 1 and 68.6± 33.3 U/L on Day 3. The mean ALP levels were 155 ± 85.8 U/L on Day 1 and 164 ± 94.7 U/L on Day 3, with a significant difference between Day 1 and Day 3 ALP levels.

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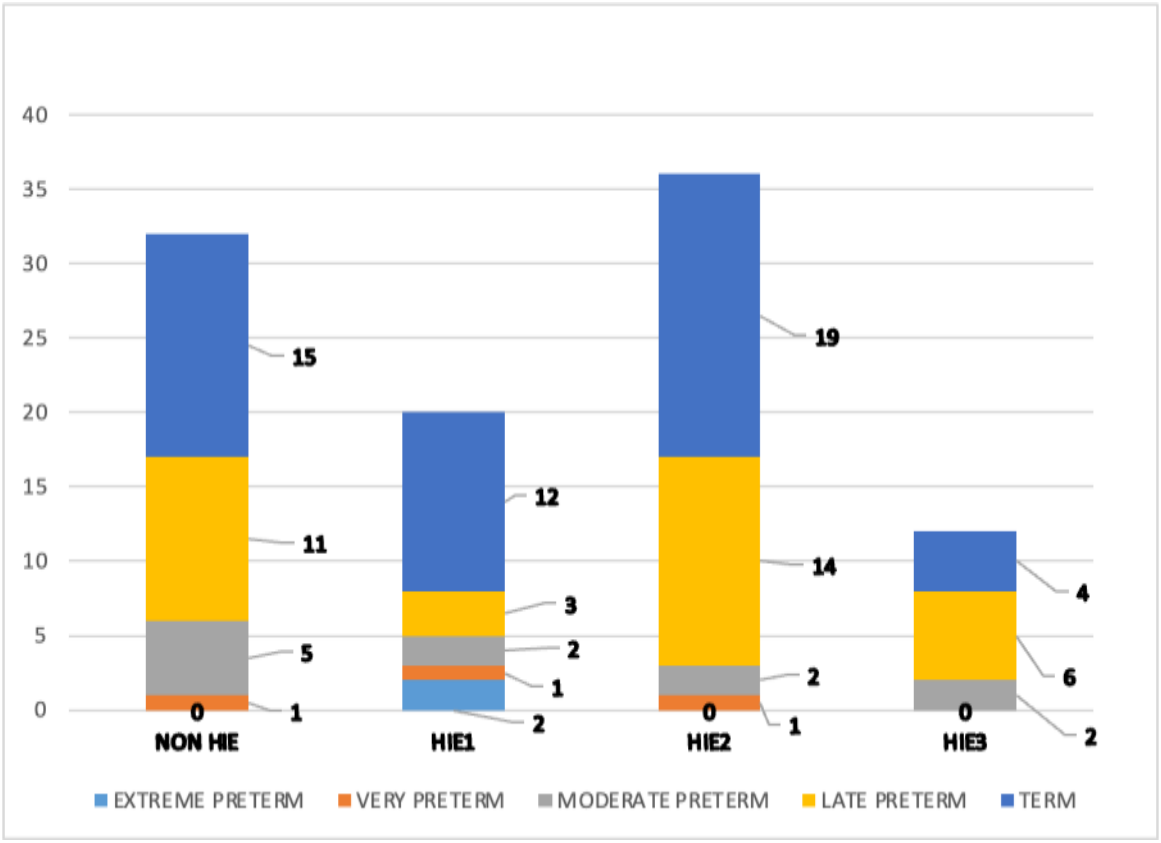

Figure 1: Distribution of study participants according to Gestational age and HIE status among asphyxiated patients

Table 2 : Mean Alt Level Of Study Participants On Day 1 And Day 3			
	TOTAL PARTICIPANTS	**MEAN (IN U/L)**	**STANDARD DEVIATION**
ALT LEVELS (day 1)	200	53.4	± 28.2
ALT LEVELS (day 3)	200	55.4	± 29.2
AST LEVELS (day 1)	200	67.5	± 31.2
AST LEVELS (day 3)	200	68.6	± 33.3
ALP LEVELS (day 1)	200	155	± 85.8
ALP LEVELS (day 3)	200	164	± 94.7

In the comparison between asphyxiated and control groups, Day 1 ALT levels were significantly higher in asphyxiated babies (68.9 ± 29.2 U/L vs. 38 ± 16.2 U/L). Similar differences were found in Day 1 AST (82.6 ± 33.7 U/L vs. 52.3 ± 19 U/L) and ALP levels (188 ± 78.2 U/L vs. 123 ± 80.5 U/L). On Day 3, ALT (72.2 ± 31 U/L vs. 38.6 ± 13.7 U/L), AST (86.7 ± 36.5 U/L vs. 50.4 ± 15.4 U/L), and ALP (201 ± 87.7 U/L vs. 127 ± 86.8 U/L) levels were significantly higher in the asphyxiated group. Statistical tests confirmed these differences ($p<0.001$).

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Table 3 Comparison Of Alt,Ast And Alp Across Asphyxia Status				
Perinatal asphyxia	**present**	**absent**	**df**	**p-value**
N	**100**	**100**		
Mean ± SD				
***Day 1 ALT**	68.9 ± 29.2	38 ± 16.2	154	<0.001
****Day 1 AST**	82.6 ± 33.7	52.3 ± 19.0	156	<0.001
*****Day 1 ALP**	188±78.2	123±80.5	198	<0.001
***Day 3 ALT**	72.2 ± 31.0	38.6 ± 13.7	136	<0.001
****Day 3 AST**	86.7 ± 36.5	50.4 ± 15.4	133	<0.001
*****Day 3 ALP**	201 ± 87.7	127 ± 86.8	198	<0.001

In 100 newborns with perinatal asphyxia, significant differences in ALT, AST, and ALP levels on Days 1 and 3 were observed based on HIE staging, as determined by one-way ANOVA and post hoc tests.

Table 4 Association of ALT,AST and ALP level of study patients on Day 1 and Day 3 with HIE staging				
Day 1				
HIE STAGING	**Non HIE(n=32)**	**HIE1(n=20)**	**HIE2(n=36)**	**HIE3(n=12)**
***ALT**	40.9± 11.14	64.4±7.41	78.8 ± 14.05	108.6 ± 49.56
P value	<0.001	<0.001	0.044	0.003
****AST**	50.4 ± 27.5	74.7 ± 13.4	97.5 ± 24.4	121.6 ± 27.6
P value	<0.001	<0.001	<0.001	<0.001
*****ALP**	97.1 + 23.7	201.2 + 40.4	220.9 + 61	220.9 + 61
P Value	<0.001	<0.001	<0.001	<0.001
Day 2				
HIE STAGING	**Non HIE(n=32)**	**HIE1(n=20)**	**HIE2(n=36)**	**HIE3(n=12)**
***ALT**	40.7± 11.4	69.6 ± 22.2	83.2 ± 21.8	113.4 ± 30.7
P value	<0.001	<0.001	0.002	0.029

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AST	51.9 ± 18.5	79.5 ± 23.6	101.0 ± 31.8	132.4 ± 19.7
P value	<0.001	<0.001	<0.001	<0.001
ALP	102 ± 27.8	203 ± 39.1	238 ± 73.5	307 ± 57.7
P value	<0.001	<0.001	<0.001	<0.001

***Across Non HIE and HIE 1 significant, Non HIE and HIE2 significant, Non HIE and HIE3 significant, HIE1 and HIE 2 significant, HIE1 and HIE3 significant.*
*** Across all four stages significant association.*
**** Significant across Non HIE and HIE1,HIE2, HIE3, across HIE1 and HIE3, and across HIE3 and HIE2.*

For Day 1 ALT, HIE0 showed higher levels than all groups, HIE1 had higher levels than HIE2 and HIE3. Day 1 AST and ALP were higher in Non HIE compared to other groups, with HIE1 higher than HIE2 and HIE3, and HIE2 higher than HIE3. No significant difference was found between Day 1 ALP in HIE1 and HIE2. While on Day 3, ALT levels in HIE0 were higher than all groups, and HIE1 showed higher levels than HIE3, with no significant difference between HIE1 and HIE2. Day 3 AST and ALP were higher in Non HIE compared to others, with HIE1 higher than HIE2 and HIE3, and HIE2 higher than HIE3. No significant difference was found in Day 3 ALP levels between HIE1 and HIE2.

ALT had 95.7% sensitivity and 88.46% specificity at cutoff value 56.3, while in case of AST and ALP, sensitivity and specificity were 94% and 78%, and 97% and 82%, respectively, with cutoff value 58.4 and 154, respectively. It was quite clear that diagnostic value was more in case of ALT (cutoff value>56.3 U/L) than the other liver enzymes (ALP and AST) in predicting perinatal asphyxia.

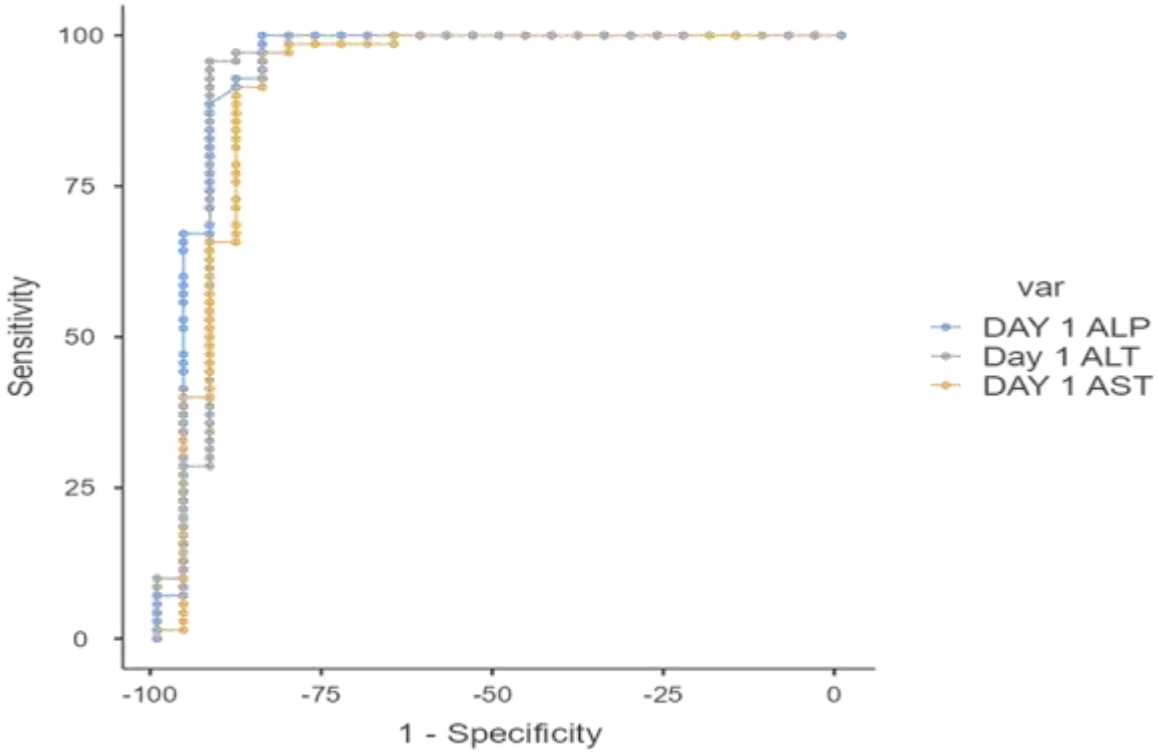

Figure 2: Receiver operator characteristics curve showing sensitivity, specificity, and area under curve of different hepatic enzymes in perinatal asphyxia.

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In ROC curve, AUC value for ALT, AST and ALP was 0.952,0.919 and 0.9, respectively, in perinatal asphyxia.

DISCUSSION-

The study delves into the impact of perinatal asphyxia on hepatic function, particularly focusing on hepatic enzyme activity, as the liver receives a significant portion of its blood supply from both the portal vein and the hepatic artery. The occurrence of Hypoxic Hepatic Injury (HHI), characterized by a surge in serum hepatic enzyme levels, reflects the hepatocellular response to hypoxia.[19-21] The enzymes, including ALT, AST, and ALP, play a pivotal role in assessing hepatocyte health. Elevations in their serum levels may signify either hepatocyte death or increased cell membrane permeability, allowing enzyme efflux into the bloodstream [20-23].

Our study meticulously examined 200 newborns, categorizing them into cases (perinatal asphyxia) and controls, with a focus on gestational age, birth weight, and gender distribution. The mean gestational age of 36 ± 2.84 weeks aligns with similar studies, establishing a robust foundation for our comparisons [21-25]. Likewise, the mean birth weight of 2.47 ± 0.537 kg mirrors findings in the literature, with slight variations attributable to regional and demographic differences[23-26]. Gender distribution in our study reveals a male predominance (54% male, 46% female), a pattern consistent with some studies but with minor variations. Furthermore, the distribution of study participants according to weight for age demonstrates a majority (77%) falling within the Appropriate for Gestational Age (AGA) category [25-28].

The severity of perinatal asphyxia was classified using Levene's classification, revealing various degrees of Hypoxic Ischemic Encephalopathy (HIE) in asphyxiated patients. The association between gestational age, birth weight, and the occurrence of asphyxia aligns with existing literature, confirming the intricate relationship between these factors [27-28]. Analyzing hepatic enzyme levels (ALT, AST, and ALP) on days 1 and 3 post-birth provides valuable insights. The stability in ALT levels suggests a resilience in hepatocellular function, while the minor fluctuations in AST levels may indicate a mild impact on mitochondrial activity. Notably, ALP levels exhibited a statistically significant increase on day 3, suggesting a delayed response to perinatal asphyxia [26-28].

Comparative analyses with other studies reinforce the robustness of our findings. Similarities in gestational age, birth weight, and gender distribution underscore the consistency of our results within the broader scientific context. Notably, our study contributes nuanced insights into the dynamics of hepatic enzyme activity, particularly during the critical postnatal period following perinatal asphyxia [25-28]. Examining the association between hepatic enzyme levels and the severity of HIE stages reveals intriguing patterns. Elevated ALT, AST, and ALP levels correlate with higher HIE stages, emphasizing the potential utility of hepatic enzymes as markers of asphyxia severity [22-26].

The detailed examination of hepatic enzyme dynamics provides a deeper understanding of the hepatic response to hypoxia. The clinical implications of our findings lie in the potential use of hepatic enzymes as early markers of HHI in neonates with perinatal asphyxia. However, the limitations, such as the relatively small sample size and single-center nature of the study, should be acknowledged. These findings contribute valuable insights to the existing body of knowledge, paving the way for further exploration into the mechanisms and clinical implications of hepatic involvement in perinatal asphyxia.

CONCLUSION

The study's primary focus was to understand the prevalence and implications of hepatitis in newborns grappling with birth asphyxia. The findings were compelling, indicating that a staggering 68% of newborns with birth asphyxia exhibited signs of hepatitis. This statistic, while striking, marked only the beginning of a more intricate exploration into the heterogeneity of the condition. Significant variations were noted in ALT, AST, and ALP levels, offering a potential stratification tool to assess the severity of perinatal asphyxia. Birth asphyxia, as the study contends, continues to be a significant contributor to perinatal mortality in developing nations, where challenges in obstetric care and neonatal resuscitation persist. The hepatic enzymes, particularly

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ALT, are proposed not only as diagnostic markers but also as crucial pieces of evidence in cases where birth history is incomplete or poorly documented.

The focus on ALT, AST, and ALP, while informative, leaves room for future research to explore a more comprehensive panel of liver function tests. Additionally, the indirect correlation with mortality and other HIE outcomes highlights the avenue for future investigations to establish more direct links between hepatic complications and clinical outcomes.

In conclusion, the study on hepatic enzymes in newborns with birth asphyxia unveils a tapestry of complexities. From the prevalence of hepatitis to the nuanced interplay of gestational age, gender dynamics, and hepatic enzyme dynamics, each thread contributes to a more profound understanding of perinatal asphyxia. ALT, standing out as a diagnostic powerhouse, holds promise for reshaping clinical approaches to early identification and intervention.

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