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Original Research Article

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A study in early neonatal period for the outcome based on the hepatic involvement following severe birth asphyxia in full term neonates

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ABSTRACT

Background: The current study is focused on assessing the liver involvement of severely birth asphyxiated newborns, by measuring liver enzymes like Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) to predict the outcome of those babies.

Methods: Total 111 severely birth asphyxiated newborns were assessed in a hospital based prospective analytical study. Liver enzymes were measured for all babies included in the study. Study subject details were obtained through a pre-structured questionnaire and also morbidity and mortality were noted. Analysis of the research data was done through appropriate statistical methods using SPSS version 20.

Results: It was observed that incidence of hypoxic ischemic hepatitis, among entire study population was 34.2% (38 cases) based on SGPT (>100 U/I) values. Current study findings indicated that incidence of hypoxic ischemic hepatitis had a positive correlation with hypoxic ischemic encephalopathy (HIE) staging. Mean SGOT, SGPT values were observed to increase as the HIE staging progressed. Based on Spearman's correlation coefficient evaluation, it was determined that the elevated SGOT and SGPT values had moderate positive correlation with HIE, seizure, ventilator support and death in the study population. It was found from the present study findings that statistically significant mortality (77.4%) was observed among the HIE stage III babies, with elevated SGPT values.

Conclusions: Current study findings revealed that elevated SGOT and SGPT values (more than twice the normal) has high sensitivity to predict the outcome in severely birth asphyxiated newborns. The stated parameters can prove to be effective in counselling parents regarding morbidity and mortality of neonates due to birth asphyxia.

Keywords: Birth asphyxia, SGOT, SGPT, HIE, Neonates, Mortality, Morbidity

INTRODUCTION

Asphyxia means inadequate oxygen and blood supply to vital organs of body. Birth asphyxia occurs when a neonate' organs do not get adequate blood and oxygen supply before, during or after birth. During parturition, blood supply to the maternal placenta is interrupted due to uterine contraction, causing a transient decrease of oxygen in the fetal blood leading to HIE. When placental

(prenatal) or pulmonary (immediate post-natal) gas exchange is declined or ceased, there is partial or complete lack of oxygen to fetus vital organs. Fetus compensate for the fall in blood and oxygen supply with redistribution of cardiac output mainly to vital organs like brain, heart and adrenals at the expense of other organs like liver, lungs, skin, muscle, bowel and kidneys leading to multi organ dysfunction (MOD).³ Hypoxic ischemic encephalopathy may lead to cell injury followed by cell

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death which can be either necrotic or apoptotic. When a cell is exposed to hypoxic ischemic insult, consequences depend on duration and degree of insult. If the hypoxic ischemic insult (HI) is brief, cellular injury may be reversible, but with severe HI, the cell is irreversibly damaged.^{4,5} The irreversibly damaged cells undergo cell death by necrosis and apoptosis. Clinical signs involving

CNS after perinatal asphyxia is called HIE. Severity of HIE is graded as; HIE I (mild), HIE II (moderate) and HIE III (severe).⁶ HIE staging correlates with neurological outcome. The detailed classification for HIE staging was first done by Sarnat & Sarnat with scoring of 0-22.⁷ This was simplified by Levene's by assessing HIE only for consciousness, tone, seizure, reflexes (Table 1).⁸

Table 1: Levene's HIE classification.8

Feature	HIE stage I, mild	HIE stage II, moderate	HIE stage III, severe
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe
Seizure	No	Yes	Prolonged
Suck/respiration	Poor suck	Unable to suck	Poor respiration efforts

Birth asphyxia is a leading cause of neonatal mortality worldwide resulting in 24% of neonatal death. 25% of perinatal asphyxia survivors are left with permanent neurologic deficits. Occurrence of perinatal asphyxia is higher in developing countries; birth asphyxia is the cause of 20% neonatal deaths in India. 9-11

Each baby may exhibit different symptoms of birth asphyxia, the most common symptoms include; abnormal heart rate, increased blood acid levels, pale skin colour and weak breathing. Tests that are used to diagnose birth asphyxia are, determining pH of blood; pH less than 7.00, in the arterial blood of the umbilical cord is an indicative of asphyxia. APGAR score is reported as a clinical marker for the identification of perinatal asphyxia. APGAR test scores are based on neonate's skin colour, heartbeat, reflexes, muscle tone and respiration. APGAR score of 0-3 for longer than 5 minutes is considered as an indicative of asphyxia.12 Asphyxia is associated with multi organ dysfunction which is indicated by occurrence of neurological problems such as seizures, coma, respiratory distress, low blood pressure or other problems in circulatory, digestive and respiratory systems. Due to HI in birth asphyxia, cell injury occurs and the injured cells leak intra cellular enzymes like alanine transaminase, aspartate transaminase, dehydrogenase, troponin, creatinine phosphokinase. 13,14 Measurement of these enzymes in plasma is used as a potential predictor to grade HIE and predict birth asphyxia. If the fetus is subjected to chronic hypoxia and/or insufficient nutrition for a longer period of time it would be manifested by growth retardation and decreased amniotic fluid which can be detected by antenatal ultrasound, however sensitivity of using such clinical risk scoring as a predictor of fetal asphyxia is very low. 15-19

Birth asphyxia and its severity is difficult to predict. In the present study attempts were being made to find out the correlation of HIE staging with hepatic involvement and correlation of hypoxic ischemic hepatitis with mortality in severe birth asphyxia, thereby assessing whether the hypoxic ischemic hepatitis can be used as the prognostic indicator for HIE and death due to birth asphyxia.

METHODS

Study place and duration

The study was carried out at neonatal ward of tertiary care hospital of government medical college. Patients admitted between 1 February 2013 to 31 July 2014 were included in the study after taking informed consent.

Study population

The study population comprised of all neonates with severe birth asphyxia, admitted to neonatal intensive care unit in department of paediatrics.

Study design

Current study is a hospital based prospective analytical study.

Sample size

111 severely asphyxiated newborns were selected as study subjects. The sample size was calculated using formula mentioned below;

Sample size, $n = 4pq/d^2$

Where p is proportion (40% of severe birth asphyxia), q=1-p and d=9% (error of margin)

Inclusion criteria

Full term neonates (age between 37 to 42 weeks) with APGAR score <3 at 10 minutes of birth.

Exclusion criteria

Preterm neonates (gestational age <36 weeks), maternal chorioamnionitis, maternal viral hepatitis, congenital

abnormalities including subtle dysmorphism of unknown significance or a major anomaly of a single organ, haemorrhagic shock without evidence of intrapartum asphyxia, cranial birth trauma and meconium aspiration syndrome.

Study protocol

Informed consent from the parents and care givers were obtained for including the neonates in this study. A structured questionnaire was made to note a detailed history and neurological examination. Baby was thoroughly examined. HIE staging was done by using Levene's scoring. Details of the gestational age, mode of delivery, sex of the baby, mode of resuscitation, APGAR score, seizure if any, and details of mode of ventilation were documented. Clinical progression of the neonates was closely observed. Venous blood sample was taken on first day after 2 hours of life for all newborns included in the study. Blood samples of newborns were analysed of liver enzymes (SGOT, SGPT, and ALP). Follow up were taken on day 1 and day 3 to determine liver enzymes, HIE stage, seizure, inotrope support, ventilator support and mortality for the first seven days of life. Mortality occurrences were noted down in the proforma.

Statistical analysis

Study data were analysed using statistical package for social sciences (SPSS software) version 20. Study variables were divided into categorical and continuous variable according to the nature of the data. The continuous variables like liver enzymes were converted into categorical variable for the analysis purpose. Data was analysed using chi-square and Mann Whitney test, taking p<0.05 as the level of significance.

RESULT

Total 111 neonates fulfilled the inclusion criteria in the mentioned study period, thus data of these one hundred and eleven subjects were analysed and presented. Out of total 111 subjects, 49 (44%) newborns were males and 62 (56%) were females. Out of the selected study group 45% babies were born through normal delivery, 47.7% were born through lower segment caesarean section (LSCS) method and 7.3% of babies were born through forceps delivery. Statistical analysis of current study findings revealed that there is no significant association between mode of delivery and HIE. Out of the total study group of birth asphyxia, 40% of the study population belonged to hypoxic ischemic encephalopathy (HIE) grade III (severe) and other 60% were categorized under the grades HIE I and II (non-severe) (Figure 1).

Among the selected study population 48.6% of neonates with birth asphyxia had SGOT values >100 U/L and 51.4% depicted SGOT values <100 U/L. SGOT values >100 U/l were observed more in neonates in HIE stage III compared to neonates belonging to HIE stage I and II.

Mortality rate was observed to be high in study population having the SGOT values >100 U/I (Table 2). Results of SGPT test revealed that SGPT values >100 U/l were seen more in neonates in HIE stage III in comparison to babies belonging to HIE stage I and II. 34% of study population exhibited SGPT values >100 U/L and 66% showed SGPT values ≤100 IU/l (Table 2). The mortality was observed to be high in study population having the SGPT values >100 U/l. Statistically significant correlation was observed between HIE staging and mortality rate (p=0.0001) (Table 3). Out of total 111 neonates in the study population 72 severely asphyxiated newborns, required ventilator facility. It was also observed that ventilator support was needed more for HIE stage III group compared to HIE stage I and II. It was observed during the study that 65.8% of the study population needed inotrope support to maintain circulation and a greater number of deaths was documented in HIE III with inotrope support compared to HIE stage I and II without inotrope support.

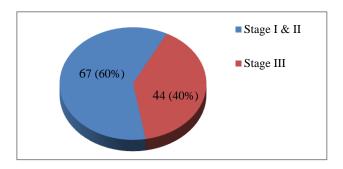


Figure 1: HIE staging of study population.

64.9% of study population had seizures within the study period. Seizures and mortality were documented more in HIE group III compared to other groups. It was also observed that some babies of HIE stage III died earlier without developing seizure (Table 4). 43.2% of study population was observed to have jaundice. Statistical analysis of study findings, post birth of study subjects at day 1 and day 3, revealed that there was a moderate positive correlation seen between SGOT, SGPT levels with HIE, mortality, seizure and ventilator support.

Prediction of HIE severity using SGOT levels through ROC curve

Receiver operating characteristic (ROC) curve was constructed to predict HIE severity from SGOT levels; obtained area under the curve (0.878) was with narrow confidence interval. The cut off for high sensitivity and low false positivity in the coordinates of the ROC curve was 85.5 U/l. Taking SGOT values >86, 2×2 table was constructed to indicate HIE severity. Clinically assessed Levene's HIE staging was used as a reference test. It was observed that SGOT cut off level of 85.5 U/L has high sensitivity and negative predictive value with low false negative value (Table 5 and Figure 2).

Prediction of HIE severity using SGPT levels through ROC curve

Area under the curve of ROC (0.877), constructed to predict HIE severity from SGPT levels was observed to be with narrow confidence interval. The cut off for high sensitivity and low false positivity in the coordinates of the ROC curve was 85.5 IU/l. Taking SGPT values >85.5, 2×2 table was constructed to indicate HIE severity. Clinically assessed Levene's HIE staging was used a reference test. It was observed that SGPT cut off level of 85.5 U/l has high sensitivity, high specificity and high negative predictive value with low false negative value (Table 5 and Figure 2).

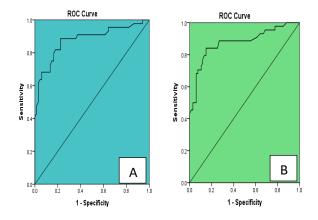


Figure 2: ROC curve for prediction of HIE severity by using (A) SGOT and (B) SGPT levels (p=0.0001).

Prediction of mortality using SGOT levels through ROC curve

Area under the curve of ROC (0.852), constructed to predict mortality from SGOT levels was found to have narrow confidence interval. The cut off for high sensitivity and low false positivity in the coordinates of the ROC curve was observed as 79.5 U/l. 2×2 tables were constructed using SGOT >80 U/l as abnormal values to indicate mortality. Clinically confirmed death was used as reference test. It was observed that SGOT cut off level of 80 U/l has high, sensitivity and high negative predictive value with low false negative value (Table 6 and Figure 3).

Prediction of mortality using SGPT levels through ROC curve

Area under the curve of ROC (0.852), constructed to predict mortality from SGPT levels was found to have narrow confidence interval. The cut off for high sensitivity and low false positivity in the coordinates of the ROC curve was observed as 68.5 U/l. 2×2 tables were constructed using SGPT >69 U/l as abnormal values to indicate mortality. Clinically confirmed death was used

as reference test. It was observed that SGPT cut off level of 69 U/l has high, sensitivity and high negative predictive value (Table 6 and Figure 3).

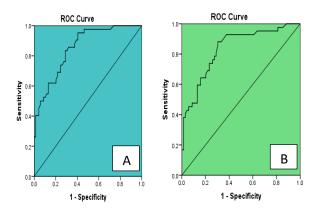


Figure 3: ROC curve for prediction of mortality by using (A) SGOT and (B) SGPT levels (p=0.0001).

Mann Whitney statistical analysis was used to correlate SGOT and SGPT values with severe and non-severe HIE patients and with survivor and non-survivor newborns. In all the cases, observed p value was less than 0.05 (Figure 4).

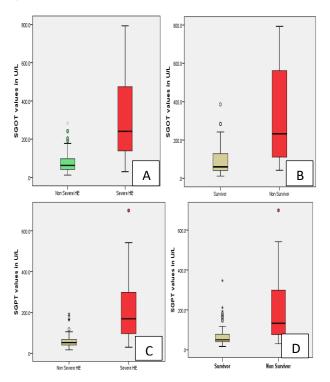


Figure 4: Correlation of SGOT values with (A) severe and non-severe HIE, (B) survivor and non-survivor newborns, correlation of SGPT values with (C) severe and non-severe HIE, (D) survivor and non-survivor newborns.

Table 2: Correlation of SGOT and SGPT values, with HIE staging and mortality.

Variables	HIE staging	Death Yes	No	_ Total
SGOT		165	110	
>100 IU/l	III	29	10	39
	I and II	5	10	15
<100 H I/I	III	1	4	5
<100 IU/1	I and II	7	45	52
Total		42	69	111
SGPT				
>100 IU/L	III	24	7	31
	I and II	3	4	7
<100 IU/L	III	6	7	13
	I and II	9	51	60
Total		42	69	111

Table 3: Correlation between HIE staging and mortality.

HIE staging	Death		Total	Total
	Yes	No	Total	10121
Stage III	30	14	44	
Stage I and II	12	45	67	
Total	42	69	111	

Table 4: Correlation between seizure and severe birth asphyxia.

Seizures	HIE staging	Death		Total
		Yes	No	Total
Yes	III	29	11	40
	I and II	11	21	32
No	III	1	3	4
	I and II	1	34	35
Total		42	69	111

Table 5: 2×2 tables constructed using SGOT and SGPT values as 85.5 U/l.

SGOT	HIE		Total
	Severe	Non-severe	
>85.5 IU/l	40	25	65
≤85.5 IU/l	4	42	46
Total	44	67	111
SGPT			
>85.5 IU/L	37	10	47
≤85.5IU/L	7	57	64
Total	44	67	111

Table 6: 2×2 tables constructed using SGOT value as 80 U/l and SGPT value as 69 U/l.

SGOT	Death		Total	Total
3601	Yes	No	Total	
>80 IU/l	40	28	68	
≤80 IU/l	2	41	43	
Total	42	69	111	
SGPT				
>69 U/L ≤69 U/L	33	20	53	
≤69 U/L	9	49	58	

DISCUSSION

In present study, overall, 3.2% incidences of severe birth asphyxia based on SGPT (>100 U/I) values in neonates were observed against total inborn admission babies (2252). 111 birth asphyxia cases were analysed for the study and the incidences reported in current study were comparable with most of the studies in India and overseas. It was observed that incidence of hypoxic ischemic hepatitis had a positive correlation with HIE staging. Out of 111 severely asphyxiated babies 44 (39.6%) cases were of HIE stage III and the remaining cases 67 (60.4%) were of HIE stages I and II.

It was concluded through current study that the incidence of severe birth asphyxia is not gender specific. Study findings also revealed that serum level of transaminase was significantly higher in non-survivor neonates in comparison to survivor neonates of birth asphyxia. Similar results of higher transaminase serum levels were reported by Saili et al.²⁰ Positive correlation was observed between the level of transaminases and the severity of HIE similar to published reports of Islam et al.²¹

Current study findings revealed that 43% of asphyxia babies had hepatic involvement which is comparable to the study reports of Tarcan et al.²¹ Hankins et al in their study reported abnormal alanine transaminase (ALT) elevation in 35% of asphyxiated babies which was similar to current study findings that showed 34% of asphyxiated babies with elevated ALT levels.²²

It was observed in present study that newborn babies with HIE exhibited higher level of transaminases which is comparable to reports published by Ruiz et al.²³ Current study findings revealed ALT ranges from 51-699 U/l in asphyxia babies which were lower than the ALT range of 446-3050 U/l reported by Goldberg et al. Even though the reported ALT range was higher than the observed ALT range in current study, the values of AST and ALT in present study findings were higher for asphyxia non survivors indicating severe HIE.^{24,25}

The study findings revealed that out of 44 HIE stage III babies, 31(70.4%) had elevated SGPT (twice more than normal values, >100 U/l) and remaining 29.6% of babies had SGPT <100 U/l. The mean SGOT, SGPT values were observed to be increasing as the HIE staging progressed. Spearman's correlation coefficient evaluation revealed that the elevated SGOT and SGPT values had moderate positive correlation with HIE, seizure, ventilator support and death in study subjects. ROC curve constructed to predict HIE severity from SGOT and SGPT level, exhibited the cut off value of >85.5 U/l with high sensitivity and low false negativity. Similarly, ROC curve constructed to predict the mortality based on SGOT and SGPT values exhibited the cut off values of >79.5 U/l and > 68.5 U/l respectively with high sensitivity and low false negative values. Among the HIE stage III babies with elevated SGPT values, statistically significant mortality of 77.4% was observed.

Limitations of study

There was no control group taken in the study. Autopsy was not done for the non survivors. More sensitive LDH level was not measured.

CONCLUSION

Perinatal asphyxia is an important cause of neonatal death. Prevention of birth asphyxia is better than its management as it is associated with MODs and has 100% mortality. Health workers have to face most of the cases of birth asphyxia in delayed and multiple tricky complicated situations, thus timely management and intervention plays a major role in treatment. Based on current study findings serum biochemical parameters like, SGOT and SGPT are proven to be more than twice higher sensitive to predict the outcome in neonates with birth asphyxia and thus can help in counselling the parents regarding morbidity and mortality. Hence it can be concluded through the current study that serum biochemical parameters like, SGOT and SGPT can help in prompt diagnosis leading to resuscitative management measures like fluid, inotrope, IV antibiotics. antiepileptics and effective continuous fetal monitoring that can improve the outcome in birth asphyxia. As these biochemical tests have high sensitivity and are of low cost, they can be considered as potential screening tests for predicting HIE and its outcome.

Recommendations

Perinatally asphyxiated neonates should be identified early and resuscitated accordingly. Continuous monitoring for adequate hydration, oxygenation and judicious use of IV fluids should be done to maintain tissue perfusion and prevent damage to tissues. Enzyme values should be monitored and if values keep on elevating during serial evaluation, high mortality can be predicted. SGPT values with >69 U/L can be used as reference for mortality. SGPT and SGOT values more than twice the normal has good sensitivity to predict the outcome of birth asphyxia and thus should be considered in counselling parents regarding morbidity and mortality.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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