Original Article

Association between Serum Calcium Level and Hypoxic-ischemic Encephalopathy (HIE) Stages in Term Neonate with Perinatal Asphyxia

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Abstract:

Background: Perinatal asphyxia (PNA) is a devastating clinical condition because it causes permanent brain damage, even death of the newborn. Perinatal asphyxia is a common neonatal problem in our context. There is a need to identify neonates with PNA who will be at high risk for hypoxic ischemic encephalopathy and multi-organ dysfunction. **Objective:** To evaluate the association between serum calcium level and hypoxic-ischemic encephalopathy (HIE) stages in term neonate with perinatal asphyxia. **Methods:** A cross-sectional study was conducted in the Department of Paediatrics, Comilla Medical College Hospital, Comilla from January 2016 to July 2016. A total of 60 neonates of perinatal asphyxia with HIE of different stages were selected as cases. The gestational age was determined by regular last maternal menstrual date and New Ballard Scoring System. The perinatal asphyxia was diagnosed by using APGAR score and hypoxic ischemic encephalopathy was defined by Sarnat and Sarnat staging. Serum calcium was measured by photometric colorimetric test (OCPC method, orthocresol - phthalacin-complex) using AnatronAnalyte 100 Electrolyte Analyzer. Chi-square test and ANOVA test was used to see the correlation between serum calcium and different stages of HIE. **Results:** Total 60 patients were included in this study, out of them 13.3 % had HIE stage I, 75% HIE stage II , 11.7% HIE stage III. Among the pt. with HIE staging in stage I, stage II and stage III had 37.5%, 71.1% and 100% of low calcium level respectively which was statistically significant. The study also showed mean ± SD serum calcium level was 9.17 ± 1.04; 8.32 ± 1.09 and 7.73 ± 0.86 in stage I, stage II and stage III respectively. There was statistically significant lower mean level of serum calcium levels observed with severity of different HIE stages ($p< 0.05$). **Conclusion:** Thedegree of lower serum calcium is associated with the severity of the Hypoxic Ischemic Encephalopathy (HIE) stages in neonates with perinatal asphyxia and may be used as a good, simple screening test for the early assessment of HIE stages.

Key Words: Perinatal Asphyxia, Hypoxic Ischemic Encephalopathy, Serum Calcium, Neonate.

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Introduction:

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality. Globally, hypoxia of the newborn is estimated to account for 23% of the 4 million neonatal deaths each year.[1] An estimated 1 million children who survive from birth asphyxia live with chronic neurodevelopmental morbidities, including cerebral palsy, mental retardation, and learning disabilities. Perinatal asphyxia is defined by the World Health Organization (WHO) as "the failure to initiate and sustain breathing at birth." The WHO definition of birth asphyxia in the International Classification of Diseases (ICD-10) is based on the Apgar scoring system. An Apgar score at 1 min of 0-3 defines severe birth asphyxia and an Apgar score of 4-7 defines mild and moderate birth asphyxia.[2] Recent studies indicate an incidence of about 1.0-1.5 % in most centers which is usually related to gestational age and birth weight.[3]In a study in Bangladesh, incidence of perinatal asphyxia was found to be 9.76 per 1000 live birth.[4]As a result of placental insufficiency 90% of asphyxial insults occur in the antepartum or intrapartum periods, resulting in an inability to provide

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O2 to and remove CO2& H+ from the foetus.[5] The remainder are postpartum, usually secondary to pulmonary, cardiovascular or neurologic insufficiency.[3]

Intrauterine growth restriction with increased vascular resistance may be the 1st indication of fetal hypoxia.[6] At delivery, the presence of meconium-stained amniotic fluids evidence that fetal distress has occurred.[6] At birth, affected infants may be depressed and may fail to breathe spontaneously.[6] Pallor, cyanosis, apnea, a slow heart rate, unresponsiveness to stimulation and seizure are also the signs. Though most often seizure occurs as a result of the hypoxic-ischemic encephalopathy (HIE), in asphyxiated newborns it may also be due to hypocalcemia, hypoglycemia or infection.[6] In asphyxia, two features useful in predicting outcome include the duration of neural abnormality and presence of seizure.[5] Perinatal asphyxia may lead to adverse effects on all major body systems in a term neonate including renal, neurologic, cardiac and lung dysfunction in 40%, 31%, 25% and 23% cases respectively.[7] When the asphyxial insult is followed by clinical evidence of abnormal neonatal neural behaviour, the syndrome is described as hypoxic-ischaemic encephalopathy (HIE).[5] HIE is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay.[6] Sarnat and Sarnat introduced a grading system to describe the neurological abnormality, which has been modified by Levene MI.[8,9] The outcome of neonates with different HIE grades, it appears that stage I (mild HIE) doesn't confer an increased risk of death or disability.[10] Significant reduction in intelligence quotient at 8 years has been reported in children who had suffered from grade II HIE but who were neurologically normal, compared to children with grade I HIE.[11] At stage III outcome is about 50% death; remainder with severe sequelae.[8]

A variety of metabolic problems are present in asphyxiated infants, including hyponatraemia, hypoglycaemia, hypocalcaemia and hypomag nesaemia.[12] Some of these biochemical disturbances may trigger seizure or potentiate further brain damage in asphyxiated neonates.

Asphyxiated infants with 1-minute Apgar score of 6 or less had lower serum calcium concentration than infants with 1-minute Apgar score of 7 or more, even when gestational ages were taken into consideration.[13] Perinatal asphyxia appears to play a role in neonatal calcium homeostasis.[13,14] Serum level of calcium tend to drop due to hypoxic ischemic damage to the parathyroid glands.[15,16] As a result, Hypocalcaemia is a common metabolic alteration in the neonatal post asphyxial syndrome.[14]

In asphyxiated neonates, clinically it is often not possible to distinguish the effect of hypocalcaemia from hypoxic ischaemic encephalopathy. So, for the management of these babies, the monitoring of the serum calcium level is important. Study done by PallabBasuet al. found that hyponatremia and hypocalcemia developed in asphyxiated infants compared to non-asphyxiated infants.[17]Deepak Jajoo et al. came to a conclusion that serum calcium level were significantly lower in term appropriate for gestational age infants who had history of birth asphyxia.[14]There is little information on this topic in our literature despite the fact that perinatal asphyxia is a leading cause of neonatal morbidity and mortality in our country.

Methods:

This Cross sectional study, was conducted in the Department of Pediatrics, Comilla Medical College Hospital, Cumilla, during January 2016 to July 2016. A total of 60 patients selected purposively, who were enrolled for this study after fulfiling the inclusion criteria. The study population consisted of fullterm (≥ 37 weeks gestation) newborn babyhavingbirth weight 2500 grams to 3999 grams, diagnosed as perinatal asphyxia based on Apgar score and different stages of HIE were defined by Sarnat and Sarnat staging. Pre term neonates (<37 weeks of gestation), small- for-gestational age (SGA) infants, babies with congenital malformations, suspected metabolic disease were excluded from the study. Babies, those born to mothers receiving general anesthesia, pethidine, pheno barbitone, magnesium sulphate and other drugs likely to cause depression in babies, mothers with history of febrile attack within 2 weeks before delivery were also excluded from the study. Informed written consent was taken from parents/guardians before enrollment. All the patients were examined within 24 hours of admission. The gestational age of all neonates were determined by regular last maternal menstrual date, physical examination and modified New Ballard scoring system. For estimation of serum calcium , 3 ml blood were drawn from peripheral vein before any I/V fluid or any medication. Serum total calcium was estimated by photometric colorimetric test (OCPC method, orthocresol- phthalacin- complex) using AnatronAnalyte 100 Electrolyte Analyzer in the same laboratory. Information obtained were stored in Microsoft excel sheet for analysis. Chi square test and ANOVA test were performed to evaluate the relationship between serum calcium with different stages of HIE. The statistical analysis was performed using the Statistical Package for Social Service (SPSS) version 16.0 for Windows.

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Results:

Table-I: Distribution of mothers by antenatal check up

Antenatal check up		Frequency	Percent
Yes	Regular	14	23.3
	Irregular	08	13.3
No		38	63.3
Total		60	100.0

Table 1 shows the distribution of antenatal checkup of mothers. Among all, majority, i.e. 38 (63.3%) mothers did not get antenatal checkup, whereas, 22 (36.7%) mothers got antenatal checkup, among them 14 (23.3%) mothers got antenatal checkup regularly and 8 (13.3 %) mothers got antenatal checkup irregularly.

Table-II: Distribution of mode of delivery

Mode of delivery	Frequency	Percent
NVD	44	73.3
LUCS	16	26.7
Total	60	100.0

Among the 60 cases 44 (73.3%) neonates were delivered normally and 16 (25.7%) were delivered by cesarean section.

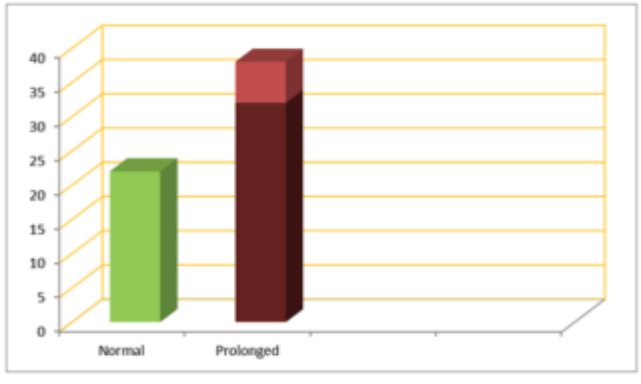

Fig-1: Distribution of stage of labour (n=60)

Among 60 patients, 22 (36.7%) patients were in Normal stage of labour and 38 (63.3%) were prolonged labour. Among prolonged labours, 32 (84.2%) patients were in prolonged 1st stage of labour and 6 (15.8%) patients were in prolonged 2nd stage of labour.

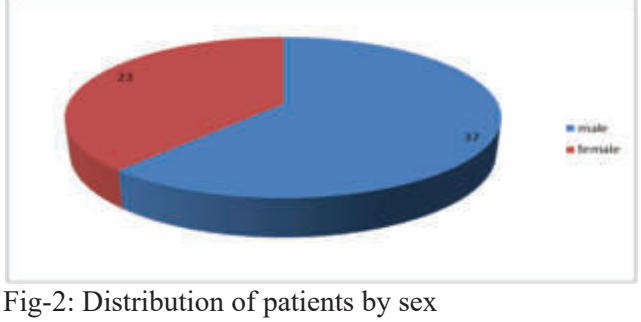

Fig-2: Distribution of patients by sex

Out of 60, male were 37 (61.7%) and female were 23 (38.3%) and male & female ratio was 1.61: 1.

Table-III: Distribution of patients by APGAR score (n=60)

APGAR score	Frequency	Percent
At 1st minute		
≤5	54	90.0
>5	6	10.0
At 5th minute		
≤5	34	56.7
>5	26	43.3

Table 3 shows the distribution of APGAR score. Among all, 54 (90.0%) patients were less than or equal to 5 APGAR score group at 1st minute and 6 (10.0%) patients were more than 5 APGAR score group at 1st minute. Whereas 34 (56.7%) patients were less than or equal to 5 APGAR score group at 5th minute and 26 (43.3%) patients were more than 5 APGAR score group at 5th minute.

Table-IV: Distribution of Hypoxic-ischemic encephalopathy (HIE) stages

HIE stages	Frequency	Percent
Stage I	8	13.3
Stage II	45	75.0
Stage III	7	11.7
Total	60	100.0

Table 4 shows 8 (13.3%) neonates were in stage I, 45 (75.0%) neonates were in stage II and 7 (11.7%) neonates were in stage III.

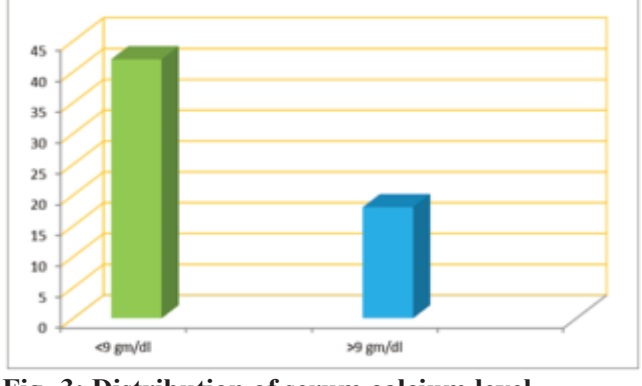

Fig.-3: Distribution of serum calcium level

Among the 60 cases of PNA 42 (70.0%) neonates serum calcium levels were found ≤ 9 mg/dl and in 18 (30.0%) neonates serum calcium levels were found more than 9 mg/dl.

Table-V: Distribution of Serum Calcium level by Hypoxic-ischemic encephalopathy (HIE) stages

Serum Calcium level	HIE stages			p value*
	Stage I	Stage II	Stage III	
≤9 mg/dl	3 (37.5)	32 (71.1)	7 (100.0)	0.029
>9 mg/dl	5 (62.5)	13 (28.9)	0 (.0)	
Total	8 (100.0)	45 (100.0)	7 (100.0)	

*Chi square test was done to measure the level of significance.

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Out of the 8 neonates in the group who had signs of HIE stage 1, 3 (37.5%) of the neonates had a serum calcium values <9mg/dl and 5(62.5%) of the neonates had a serum calcium values > 9 mg/dl. Among 45 neonates of HIE stage2, 32 (71.1%)of the neonates had a serum calcium values <9mg/dl. Out of the 7 neonatesin the group who had signs of HIE stage 3, all 7 (100%) of the neonates had a serum calcium values <9mg/dl. There was statistical significance observed between HIE stages and number of neonates with lower serum calcium level (p<0.05).

Table-VI: Mean values of Serum Calcium level by Hypoxic-ischemic encephalopathy (HIE) stages

Serum Calcium level (mg/dl)	HIE stages			p value*
	Stage I	Stage II	Stage III	
Mean ± SD	9.17 ± 1.04	8.32 ± 1.09	7.73 ± 0.86	0.035
Range	7.79-10.30	6.72-10.34	6.50-8.90	

*ANOVA test was done to measure the level of significance.

Table 6 shows in stage I, mean ± SD serum calcium level was9.17 ± 1.04; In stage II, mean ± SD serum calcium level was8.32 ± 1.09 and In stage III, mean ± SD serum calcium level was7.73 ± 0.86. There was positive association observed between lower mean level of serum calcium levels with severity of different HIE stages.

Discussion:

Perinatal asphyxia is a common neonatal problem and contributes significantly toneonatal morbidity and mortality. Birth asphyxia is a common and important preventable cause of cerebral injury and death occurring in the neonatal period. Perinatal asphyxia is a devastating clinical condition because of its potential for causingpermanent damage, even death of the fetus or newborn infant. The value of presentbiochemical markers for diagnosing asphyxia is inadequate and controversial.There are only a few studies that compare blood values of metabolites with severity ofasphyxia and different stages of HIE. A few studies conducted who have followed up the infants over a period of timehave found out that long term neurological outcome of these infants correlate well withthe severity of asphyxia and with the severity of various biochemical alterations.This study was carried out at Comilla Medical College Hospital to see the serum calcium level in infants with perinatal asphyxia. A total 60 consecutive patients of perinatal asphyxia with different HIE stages were included in the study. In the present study, an attempt has been made to evaluate the incidence of alteration of serum calcium level in birth asphyxia and to find out any association betweenthe severity of asphyxia and this alteration, so that withearly detection of these change in blood could beinstituted at the earliest so as to prevent early neonatal brain injury so that the child canhave a normal neurological outcome and can lead a productive life useful to the society.

The present study revealed, out of 60 pt. 13.3 % had HIE stage I, 75%HIE stage II, 11.7% HIE stage III. Among the pt. with HIE staging in stage I, stage II and stage III had 37.5%, 71.1% and 100% of low calcium level respectively which was statistically significant These findings are similar to PallabBasu who observed the high incidence of low serum calcium in asphyxiated infants.[16] The present study also revealed, serum calcium values were significantly lower in asphyxiated neonates (8.37±1.11). which is concordance with Jajoo et al, where mean serum calcium level was 8.31±0.48 mg/dl and PallabBasu, where was 6.85±0.95 mg/dl.13,16Serum calcium levels were significantly lower in neonates with severe HIE (Stage 3) (7.73±0.86) when compared with neonates with moderate HIE (Stage 2) (8.32±1.09) and those with mild HIE (Stage 1) (9.17±1.04). A significant statistical association was detected between the levels of hypocalcaemia and the severity of HIE stages in neonates with perinatal asphyxia(p< 0.05) which is concordance with Jajoo et al, where mean serum calcium levels in severe, moderate and mild HIE were 6.817± 0.29, 7.157 ± 0.09 and 7.349 ± 0.33 respectively. 13However, we found S. calcium estimation to be a good, simple screening test for the early assessment of HIE in neonates with perinatal asphyxia and there is anassociation between the degree of lower serum calcium level and the severity of the encephalopathy, indicating the degree of injury at an early stage when other quantitative methods frequently cannot be carried out. So, through this study we found that estimating the levels of calcium would be a valuable screening test in predicting the severity of HIE in neonates with perinatal asphyxia and their levels directly indicates the degree of injury the neonate has suffered in the intrauterine environment.

Conclusion:

Infants with asphyxia have found lower calcium levels and levels decreased with the severity of HIE. Serum level of calcium might be used as an indicator for assessment of severity of birth asphyxia and severity of HIE in neonates.So, estimation of serum calcium level could be an easy and affordable test and at the same

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time early biochemical marker of birth asphyxia which biochemically correlates well with the HIE stages in neonates with perinatal asphyxia.

Limitation of the study:

The serum calcium level was measured only once when perinatal asphyxiawas diagnosed.

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