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Early Onset Hypocalcaemia in Babies Delivered at The University of Port-Harcourt Teaching Hospital, Port Harcourt, Nigeria

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Abstract

Introduction: Neonatal hypocalcaemia could be asymptomatic and potentially life threatening. Early onset type accounts for 95% of cases and can therefore be detected by screening.

Aim: To determine prevalence of Early Onset Neonatal Hypocalcaemia (EONH) in healthy and sick newborns at a tertiary health facility in Southern Nigeria.

Method: This was a prospective hospital based cross sectional study in which serum ionized calcium levels were determined for babies aged 0-72 hours, delivered and nursed in the hospital within the study period. Clinical details of mother baby pairs were obtained using a questionnaire. Data was entered into an excel sheet and analyzed using SPSS version 20.

Results: Of 384 newborns studied, there were 201 (52.3%) males and 183(47.7%) females giving a M: F ratio of 1.1:1. The mean age, Gestational Age (GA) and Birth Weights (BW) were 24 ± 19 hours, 37.99 ± 2.36 weeks and 3.15 ± 0.69 kg respectively.

Sixty-two (16.1%) had hypocalcaemia. The prevalence was highest in babies aged 25-48 hours, GA ≥37 weeks, BW 1.0-1.49 kg and severely asphyxiated babies. Hypocalcaemia however had a statistically significant association with age of neonates in hours (p=0.001) and Birth Asphyxia (p=0.002). Forty-seven (75%) of hypocalcaemia babies were asymptomatic. The commonest symptoms were jitteriness and respiratory distress.

Conclusion: The prevalence of EONH was 16.1%. It was significantly commoner in neonates with severe birth asphyxia and in neonates aged 25-48 hours and largely asymptomatic. Neonatal screening is advocated especially in high risk neonates aged 12-48 hours of life.

Keywords: Early onset; Neonatal hypocalcaemia; Prevalence

Introduction

Hypocalcaemia is a common morbidity in the newborn period and can be potentially life threatening [1]. It is defined as Early Onset Neonatal Hypocalcaemia (EONH) when it occurs between 12 and 72 hours of life or late onset occurring after 72 hours of life [1-3]. Hypocalcaemia can be diagnosed using total or ionized serum calcium level. A total serum calcium level of less than 1.75 mmol/l (7 mg/dl) in preterm or 2.0mmol/l (8 mg/dl) in term or ionized calcium level of less than 1.0 mmol/l (4 mg/dl) in both term and preterm babies [4,5].

EONH accounts for 95% of all neonatal hypocalcaemia with prevalence ranging between 15% and 30%. The prevalence varies and depends on presence of several factors such as gestational age, infant and maternal co-morbidities such as birth asphyxia, maternal diabetes and hyperthyroidism [1-6]. Hypocalcaemia may be asymptomatic or mimic other disease conditions and therefore remain unrecognized until the post seizure period when damage to the neuron may have occurred.

Documented studies on neonatal hypocalcaemia in Nigeria have been in neonates with predisposing co-morbid conditions [7,8]. In Benin, Onyiriuka [7] reported a prevalence of 22.6% in asphyxiated full term neonates in a missionary hospital while

Omene and Diejomaoh [8] reported a prevalence rate of 9.4% in asphyxiated neonates in University of Benin Teaching Hospital. Also Tsang, et al. [9,10] in United States of America (USA) reported prevalence rates of early neonatal hypocalcaemia of 37.6%, 14.3% and 29.8% in preterm, birth asphyxiated and low birth weight neonates respectively. Eghbalian [11] in a Teaching Hospital in Iran reported a prevalence of 13.8% of early onset neonatal hypocalcaemia.

In developed countries, screening for early neonatal hypocalcaemia is done routinely in the first 72 hours of life [12]. Neonatal screening has helped to identify neonates with hypocalcaemia and thus facilitated appropriate early intervention. The aim of this study was to determine the prevalence of early onset neonatal hypocalcaemia in both healthy and sick newborns at the University of Port Harcourt Teaching Hospital (UPTH).

Subjects and Methods

This was a prospective hospital based cross sectional study done over a six-month period (March 2016 - August 2016) at the University of Port Harcourt Teaching Hospital. Inclusion criteria were babies 0 to 72 hours old, delivered at 28 to 42 completed weeks of gestation and still being nursed in the Post Natal Ward (PNW) or admitted into the Special Care Baby Unit (SCBU). Extreme Low Birth Weight (ELBW) neonates less than 1000 g and those who had received oral or intravenous calcium were excluded. Using standard statistical methods, a minimum sample size of 384 was calculated for the study. Neonates in the SCBU and the PNWs who met the inclusion criteria during the study period were recruited consecutively until the sample size was achieved. At recruitment, data on socio-demographic characteristics of baby mother pairs, pregnancy and delivery were obtained and recorded using an interviewer administered questionnaire. Physical examination was done for each baby and gestational age was determined using the Ballard scoring system [13].

For each child recruited, venous blood was collected without tourniquet into titrated lithium heparin bottles placed in ice packs and transported to the laboratory. Serum ionized calcium level was analyzed within 24 hours using an ion selective electrode potentiometric machine [14,15] GENUS® 300 (GE300). Neonates with serum ionized calcium level less than 4 mg/dl (1mmol/l) were considered to have hypocalcaemia [3,4]. All neonates with hypocalcaemia were treated in conjunction with the managing teams.

Data collected were entered into a Microsoft excel sheet and analyzed using SPSS version 20. A frequency distribution was generated for categorical variables. The continuous variables were expressed as means and standard deviations. Chi square test was used to test for association between categorical variables.

Independent student's t test was used to compare the difference in means across two groups while Analysis of Variance (ANOVA) was used to compare means across more than two groups. Statistical significance at 95% confidence interval was set at p-value <0.05. Data were presented as charts, graphs and tables. Written informed consent was obtained from parents/caregivers and ethical approval for the study was obtained from Ethics Committee of the UPTH.

Results

A total of 384 babies were studied. There were 201 (52.3%) males and 183(47.7%) females giving a male to female ratio of 1.1:1. The mean age of babies studied was 24 ± 19 hours with a median age of 18 hours. The mean gestational age of neonates studied was 37.99 ± 2.36 weeks, mean birth weight was 3.15 ± 0.69 kg and mean serum ionized calcium level of 1.24 ± 0.24 mmol/l with a range of 0.61-1.71 mmol/l.

The general characteristics of neonates studied are shown in Table 1**.** Two hundred and forty-three (63.3%) were aged 0 to 24 hours, 281 (73.2%) were term, 295 (76.8%) had normal birth weight and 104 (38.2%) had birth asphyxia.

Variables	Total No	% of Total
Sex		
Males	201	52.3
Females	183	47.7
Age Category(hours)		
0 - 24	243	63.3
25 - 48	83	21.6
49 - 72	58	15.1
Gestational Age (weeks)		
<37	103	26.8
≥37	281	73.2
Birth Weight(Kg)		
1.0 - 1.49	8	2.1
1.5 - 2.49	44	11.5
2.5 - 3.99	295	76.8
≥4.0	37	9.6
Apgar Score		
Severe BA (0 - 3)	16	4.2
Moderate BA(4 - 5)	22	5.7
Mild BA (6 - 7)	66	17.2
No BA (8 - 10)	280	72.9
BA (Birth Asphyxia).		

Table 1: General Characteristics of Neonates Studied.

The mean level of serum calcium was lowest in babies aged 25 to 48 hours, preterm neonates; Very Low Birth Weight (VLBW) neonates, moderately and severely asphyxiated neonates. There was a significant association between the mean levels of serum ionized calcium with age group, gestational age and Apgar score category. Table 2 shows the mean value of serum ionized calcium for different categories of newborns.

Variables	Total No of babies	Mean serum ionized calcium level ± SD	p-value
Sex			
Males	201	1.25 ± 0.23	0.192
Females	183	1.22 ± 0.24	
Age Category (hours)			
0 - 24	243	1.27 ± 0.22	
25 - 48	83	1.15 ± 0.25	0.0001*
49 - 72	58	1.21 ± 0.23	
Gestational Age (weeks)			
<37	103	1.20 ± 0.21	0.042*
≥37	281	1.25 ± 0.24	
Birth Weight(Kg)			
1.0 - 1.49	8	1.11 ± 0.26	
1.5 - 2.49	44	1.22 ± 0.18	0.321
2.5 - 3.99	295	1.25 ± 0.25	
≥4.0	37	1.21 ± 0.22	
Apgar Score			
Severe BA (0 - 3)	16	1.07 ± 0.24	
Moderate BA(4 - 5)	22	1.11 ± 0.23	0.001*
Mild BA (6 - 7)	66	1.27 ± 0.24	
No BA (8 - 10)	280	1.25 ± 0.23	
*Statistically significant, SD - Standard Deviation			

Table 2: Mean Serum Ionized Calcium Level of Categories of Babies.

Sixty-two (16.1%) neonates had hypocalcaemia with serum ionized calcium level of less than 1.0 mmol/l. Mean age of babies with hypocalcaemia was 30 hours. Table 3 shows the Prevalence of hypocalcaemia in various categories of neonates. The prevalence of hypocalcaemia was highest in babies aged 25-48 hours, babies ≥37 weeks' gestation birth weight 1.0-1.49 kg and severe birth Asphyxia. There was however a statistically significant association between prevalence of hypocalcaemia and age of neonates in hours (p=0.001) and Birth Asphyxia (0.002) Fifteen (24.2%) neonates with EONH were symptomatic with the commonest symptoms being jitteriness and respiratory distress.

Variables	Total no of	No with Hypocalcaemia	No without Hypocalcaemia	p-value
Sex				
Males	201	31 (15.4)	170 (84.6)	0.69
Females	183	31 (16.9)	152 (83.1)	

Age category(hours)				
0 - 24	243	27 (11.1)	216 (88.9)	
25 - 48	83	24 (28.9)	59 (71.1)	0.001*
49 - 72	58	11 (19.0)	47 (81.0)	
Gestational Age (weeks)				
<37	103	12(11.7)	91 (88.3)	0.147
≥37	281	50(17.8)	231 (82.2)	
Birth Weight(Kg)				
1.0 - 1.49	8	3 (37.5)	5 (62.5)	
1.5 - 2.49	44	4 (9.1)	40 (90.9)	0.2
2.5 - 3.99	295	50 (16.9)	245 (83.1)	
≥4.0	37	5 (13.5)	32 (86.5)	
Apgar Score				
Severe BA (0 - 3)	16	7 (43.8)	9 (56.2)	
Moderate BA(4 - 5)	22	7 (31.8)	15 (68.2)	
*Statistically significant				

Table 3: Frequency and Clinical Characteristics of babies with hypocalcaemia.

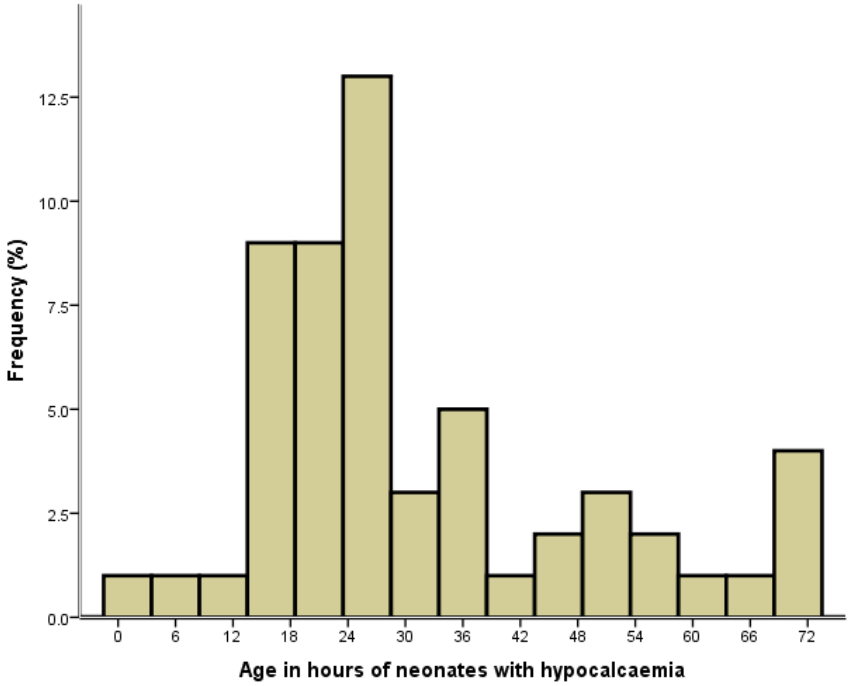

Figure 1: Frequency of hypocalcaemia according to the age of neonates.

Figure 1 shows the frequency distribution of early onset hypocalcaemia in neonates studied. Hypocalcaemia was reported in babies from age 0 to 72 hours of life however frequency of EONH was highest in babies between 12 and 30 hours of life with peak between 24 and 30 hours.

Table 4 shows the distribution of clinical features of hypocalcaemia among babies studied. 47 (75%) of babies with hypocalcaemia were asymptomatic. The commonest features recorded were jitteriness, respiratory distress in 30(7.8%) and 22(5.7%) respectively all subjects. Frequency of clinical features was however higher in babies with hypocalcaemia compared to those without in most except jitteriness.

	Hypocalcaemia		
	Present	**Absent**	**Total**
Clinical features*	**n (%)**	**n (%)**	**n (%)**
Jitteriness	6 (9.7)	24 (7.5)	30 (7.8)
Respiratory distress	6 (9.7)	16 (5.0)	22 (5.7)
Tachypnoea	2 (3.2)	5 (1.6)	7 (1.8)
Convulsion	2 (3.2)	1 (0.3)	3 (0.8)
Hypertonia	2 (3.2)	0 (0.0)	2 (0.5)
Twitching	1 (1.6)	1 (0.3)	2 (0.5)
Apnoea	1 (1.6)	1 (0.3)	2 (0.5)
Lethargy	1 (1.6)	1 (0.3)	2 (0.5)
None	47 (75.8)	265 (82.3)	312 (81.2)
*Some of the neonates had more than one clinical feature.			

Table 4: Distribution of clinical features among neonates with hypocalcaemia.

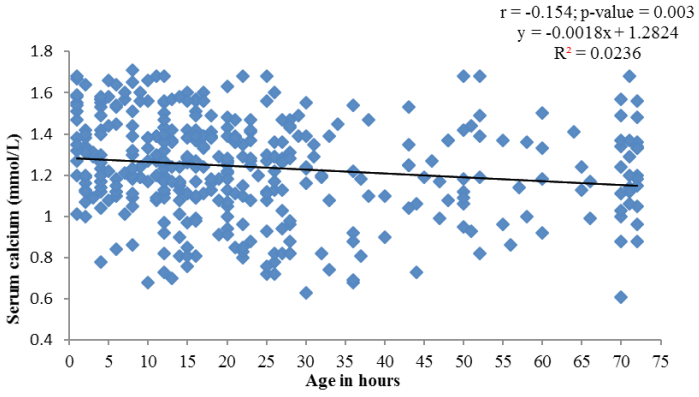

Figure 2 shows the correlation between neonatal age and serum calcium level. There was a negative linear relationship between the age in hours of the neonates and the serum ionized calcium level (mmol/L). The serum ionized calcium level decreased by 0.0018 for every one-hour increase in age of the neonate within the first 72 hours of life.

Discussion

The prevalence of Early Onset Neonatal Hypocalcaemia (EONH) in this study was 16.1%. This is comparable to 13.8% observed by Eghabalian [11] in Iran but lower than 22.6% observed by Onyiriuka [7] in Benin, 21.5% observed by Welimen [16] Kenya and 63% by Khalesi, et al. [17] in Iran.

The observed difference between the results of this present work and that of Eghabalian [11] might be due to the different method of definition of early onset neonatal hypocalcaemia. The method used in this study considered hypocalcaemia as ionized calcium level lower than 1.00 mmol/L, while that of Eghabalian [11] considered hypocalcaemia as total serum calcium less than 7 mg/dl. Ionized calcium and not total serum calcium reflects closely the functionally available calcium level that promotes neuronal functionality and is also the free and important determinant of calcium action in the body which is not dependent on total protein or acid-base balance [18]. Low total serum calcium level of less than 7 mg/dl may not necessarily indicate low ionized calcium level in the newborn, [19] therefore there could be a record of higher prevalence of hypocalcaemia when total calcium level is used.

The prevalence observed in this work was much lower than what was observed by Khalesi, et al. [17]. This is because this study focused on all newborns rather than on specific risk categories like was the case in their study. Several risk factors for early onset neonatal hypocalcaemia have been reported [7-20]. These factors include prematurity, birth asphyxia, Infant of Diabetic Mother (IDM) and low birth weight babies. The finding of the association between severe birth asphyxia and postnatal age with early onset neonatal hypocalcaemia in this present study is in consonance with the findings of earlier work by Onyiriuka [7].

In this study, the prevalence of EONH was highest in newborn aged 25 to 48 hours. This finding is supported by Onyiriuka [7]. who also found EONH prevalence to be highest at age 24 hours in his asphyxiated neonates when compared to non-asphyxiated neonates. Tsang and Oh [9] as well as Venkatereman, et al. [21] also observed a high prevalence of EONH between the ages of 25 hours and 36 hours of life which is similar to that observed in this study.

Serum calcium level is known to get to physiological nadir at the age of 24 to 48 hours in neonates [3,22]. This nadir is found to be exaggerated in preterm, asphyxiated babies and infants of diabetic mothers [9.10]. This physiologic drop in serum calcium in newborns may be related to hypoparathyroidism, end organ unresponsiveness to parathyroid hormone,[23] abnormalities of vitamin D_3 metabolism, hyperphosphatemia and hypercalcitonemia which occurs by 12-24 hours of age [24]. After birth parathyroid hormone levels increase gradually in the next 48 hours of life and

normal levels of serum calcium are regained by the third day of life [3,22]. This normal fall in serum calcium may be exacerbated with the nadir dropping to as low as 7 mg/dl (1.75 mmol/l) in very ill neonates with severe birth asphyxia, premature babies, low birth weight babies and Infants of Diabetic Mothers (IDM) increasing their risk for early onset neonatal hypocalcaemia [9,10].

Early onset neonatal hypocalcaemia was commoner in preterm in the present study although not statistically significant. In this study the reported prevalence rates of EONH in preterm and LBW babies was 11.7% and 9.1% respectively. This observed prevalence in this study is lower than that of Tsang, et al. [9,10,25] The reason for this difference in prevalence may be due to timing of sample collection as well as the gestational age of the neonates. Tsang, et al. [9,10] collected samples at 12, 24, 48, 72 and 96 hours and included neonates with GA less than 28 weeks weighing between 615 gm to 2000 gm who are at more risk for EONH. Also blood sample collection was by heel puncture and analyzed by atomic absorption spectroscopy when compared to this present study in which blood sample was collected from a peripheral vein without applying tourniquet to prevent haemo-concentration which could give a falsely raised calcium level and serum ionized calcium analyzed using Ion-selective electrode potentiometric method.

Early onset neonatal hypocalcaemia occurring within the first 48 hours of life has been reported in 20-30% of infants born before the 37th week of gestation; 30 - 40% of infants with Perinatal asphyxia (Apgar score < 7) and 30-50% of Infants of Diabetic Mothers (IDM) [26]. Twelve (11.7%) of preterm in this study had EONH in contrast to higher values reported by Eghabalian [13] and Tsang, et al. [9]. The reason for the lower incidence may be due to the smaller population of preterm relative to the number of term babies studied.

This study showed that jitteriness and respiratory distress were the most common clinical features found in neonates who had hypocalcaemia. This finding is consistent with previous studies on early onset neonatal hypocalcaemia [19,27]. Other symptoms noted were twitching, hypertonic, apneoa and lethargy which have also been reported as different clinical presentations of early onset neonatal hypocalcaemia [7,17].

The mean postnatal age of neonates who had early onset hypocalcaemia was 30 ± 18 hours (12-48 hours), while those without hypocalcaemia was 23 ± 20 (3-43 hours). By inference from this study, neonates between the ages of 12-48 hours should be screened for early onset neonatal hypocalcaemia. This is in support of the recommended time for screening for hypocalcaemia in the newborn which is 24-48 hours of life [3]. Other researcher on early onset neonatal hypocalcaemia like Onyiriuka [7] screened at 12, 24 and 48 hours of life but recommended screening should be done at 12 hours of life as most of the study population whose serum calcium concentration was normal at 12 hours maintained same at 48 hours of life.

Early onset neonatal hypocalcaemia was not uncommon in neonates aged 0-72 hours who were screened for serum ionized calcium level in the University of Port Harcourt Teaching Hospital but were largely asymptomatic.

Conclusion

The prevalence of Early Onset Neonatal Hypocalcaemia in neonates aged 0 -72 hours was 16.1%. Early onset neonatal hypocalcaemia was significantly commoner in neonates with severe birth asphyxia and in neonates aged 25-45 hours. Neonates with hypocalcaemia were largely asymptomatic and remain unrecognized because of lack of any specific ascribable associated clinical signs. Therefore, neonatal screening is advocated in high risk neonates aged 12-48 hours of life, this will lead to early recognition and prompt treatment of neonatal hypocalcaemia.

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Conflicts of Interest: There are no conflicts of interest.

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