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PREVALENCE OF NEONATAL HYPOCALCAEMIA AMONG FULL-TERM INFANTS WITH SEVERE BIRTH ASPHYXIA

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ABSTRACT

Although neonates with severe birth asphyxia are known to be at increased risk of early-onset hypocalcaemia, the magnitude of the problem is not well documented. The objective of this study was to determine the prevalence of early-onset hypocalcaemia in severely asphyxiated neonates.

In this case-control study, conducted at St Philomena Catholic Hospital (SPCH), Benin City, Nigeria, the total serum calcium concentrations of 31 full-term neonates with 1-minute Apgar score of 3 or less were measured using the O-cresulphthalein complexone method and the results were compared with those of their counterparts with 1-minute Apgar score of 7 and above. The total serum calcium concentration of severely asphyxiated neonates who received sodium bicarbonate therapy during resuscitation was compared with those of their counterparts who did not receive sodium bicarbonate therapy. All the study neonates (both the asphyxiated and the non-asphyxiated) were examined, at least, twice daily in the first 48 hours of life and their clinical findings were documented. Overall prevalence of early-onset neonatal hypocalcaemia (total serum calcium < 1.75 mmol/L) among asphyxiated neonates was 22.6%. Mean total serum calcium at the ages of 12, 24 and 48 hours were significantly lower among asphyxiated compared to non-asphyxiated neonates ($p<0.001$). The overall mean serum calcium concentrations were 1.68 $\pm$ 0.06 mmol/L (range 1.65 – 1.70 mmol/L) and 1.74 $\pm$ 0.07 mmol /L(range 1.74 – 1.77 mmol/L) in neonates treated with bicarbonate and those without bicarbonate therapy respectively ($p<0.01$). Asphyxiated neonates with normal total serum calcium concentrations at the age of 12 and 24 hours maintained this normocalcaemia at the age of 48 hours. The commonest clinical finding among asphyxiated neonates with early-onset hypocalcaemia was convulsion (57.1%). Carpopedal spasm was not a prominent clinical manifestation. Hypocalcaemia was common in the first 48 hours of life in asphyxiated neonates, particularly if they received bicarbonate therapy during resuscitation. Asphyxiated neonates whose serum calcium concentration was normal at the age of 12 hours tended to maintain this normal level at the age of 48 hours.

Key words: neonatal hypocalcaemia, birth asphyxia, bicarbonate therapy.

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INTRODUCTION

Early-onset neonatal hypocalcaemia (hypocalcaemia occurring within the first 48 - 72 hours of life) [1,2] accounts for 95% of all cases of neonatal hypocalcaemia [3]. It is related to the abrupt cessation of transplacental supply of calcium from the mother to the foetus. The healthy term infant experiences a physiological nadir in serum calcium between the age of 24 and 48 hours after which normal serum calcium levels are regained [4,5]. This normal pattern may be exacerbated with the nadir dropping to hypocalcaemic levels in neonates who have suffered severe birth asphyxia [3,4]. Tsang and Oh [6] reported a lower total serum calcium value at the age of 8 hours prior to the actual development of hypocalcaemia at the age of 29 hours.

The pathogenetic mechanism by which birth asphyxia causes hypocalcaemia is poorly understood. However, it has been speculated that delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, transient functional hypoparathyroidism, target organ unresponsiveness and sodium bicarbonate therapy may play a role [2,5,7]. Of the total serum calcium, 40% is protein-bound, 10% is complexed with anions, such as citrate, sulphate, bicarbonate, phosphate and lactate and 50% is the free or ionized physiologically active form [2,4]. Changes in plasma protein concentration alter the total serum calcium concentration in the same direction as the protein concentration [4]. In neonates, it is unlikely that a change in the concentration of plasma protein that will significantly affect the total serum calcium concentration can occur in less than one week after birth [8].

Hypocalcaemia is defined as total serum calcium less than 1.75mmol/L in all infants including preterm infants; less than 2.0mmol/L in full-term infants and less than 2.2mmol/L in children and adolescents [9].

Information on the overall prevalence of neonatal hypocalcaemia is scarce in Nigeria, especially as it relates to birth asphyxia. Tsang et al, [10,11] in two separate studies reported a prevalence of 37.6% for preterm infants and 14.3% for infants with birth asphyxia. In a retrospective study in Benin City, Omene and Diejomaoh [12] reported a prevalence of 9.4% among their asphyxiated neonates. In that study, they did stated the method used in measuring total serum calcium concentration. Early-onset neonatal hypocalcaemia is often asymptomatic [7]. When symptoms and signs are present, they tend to be non-specific and mimic many other neonatal disorders such as hypoglycaemia, hypomagnesaemia, septicaemia, opiate withdrawal syndrome, and anoxic brain injury [13,14]. From the foregoing, it is obvious that there is a need for mandatory serum calcium determination in high-risk neonates to improve their perinatal health. Indeed, Speidel et al [4] recommended that

serum calcium concentration should be determined in all neonates with encephalopathy. However, routine sampling may not be feasible in resource-limited countries.

In Nigeria, birth asphyxia still remains a major cause of neonatal death and childhood disability. National estimates indicate that birth asphyxia is the commonest cause of neonatal mortality, accounting for 26% of all cases [17]. For each asphyxia-related neonatal death, many more neonates are left with permanent disabilities. A study from a secondary health-care facility in Nigeria reported a birth asphyxia prevalence of 84 per 1000 live-births and accounted for 20.9% of all admissions into their neonatal unit with a case fatality rate of 15.7% [18]. The present study sought to determine the prevalence of early-onset neonatal hypocalcaemia among asphyxiated neonates seen in a secondary health-care institution. This will highlight the magnitude of the problem and the need to be alert towards its occurrence.

MATERIALS AND METHODS

The study population consisted of full-term neonates with severe birth asphyxia (1-minute Apgar score of 3 or less) delivered at St. Philomena Catholic Hospital (SPCH), Benin City between 1st June 2007 and 31st May, 2008. The control group was made up of full-term neonates with 1-minute Apgar Score of 7 or more delivered in the same hospital during the same period. Birth weights of neonates in both groups were appropriate for gestational ages. The study protocol was approved by the hospital authority and consent was obtained from each of the mothers after explaining to each of them that those neonates found to have low serum calcium concentration will given appropriate therapy. Exclusion criteria included: (i) death within 48 hours of age; (ii) infants of diabetic mother; (iii) infants who required exchange blood transfusion; (iv) infants on frusemide (lasix) and

(v) admission after age of 48 hours. Using O-cresulphthalein Complexone Method of Baginski et al, [17] serial total serum calcium concentration were determined at 12, 24 and 48 hours of age. Thus, three samples per subject was analysed for total serum calcium. To avoid venous stasis and eliminate artefactual haemoconcentration, blood sample was collected (without applying a tourniquet) using the open-ended needle method recommended by Wilkinson and Calvert [18]. Each of the blood samples was processed within 24 hours of collection. Infants with two sequential total serum calcium values less than 1.75 mmol/L were considered to have significant hypocalcaemia and were treated with intravenous or oral calcium gluconate. No calcium supplement was given before the first serum calcium measurement. The corresponding serum albumin concentration was determined for each blood sample used for serum calcium measurement.

Maternal age and parity as well as the infants' birthweight were recorded. Whether or not sodium bicarbonate was administered during resuscitation was noted. Both groups of neonates were examined, at least, twice daily in the first 48 hours of life and the findings were documented.

Neonates with 1-minute Apgar score of 6 and below were deemed to have had birth asphyxia. Student's t test was used in assessing the significance of the results which was set at $p<0.05$.

RESULTS

One hundred and twenty nine (9.5%) of 1,364 live-births had 1- minute Apgar score of 6 or less.

Of the 129 infants, 38 (29.5%) had 1-minute Apgar score of 3 or less (severe birth asphyxia) and they constituted the study population. More males (61.1%) than females (38.9%) suffered severe birth asphyxia with a ratio of 1.6:1.

Mean birth weight of severely asphyxiated and non-asphyxiated infants was 3.25 $\pm$ 0.54 kg versus 3.30 $\pm$ 0.33 kg $p>0.05$ respectively.

Seven out of 31 (22.6%) of asphyxiated neonates and three out of 38 (7.9%) of control neonates had hypocalcaemia with an odd ratio of 2.7 (95% CI = 0.90 – 2.91). As shown in Seven (18.4%) of the 38 severely asphyxiated babies died within the first 48 hours of life. Four out of the 7 deaths had bicarbonate therapy and low serum calcium concentration at 12 and/or 24 hours before their death.

The mean maternal age of severely asphyxiated and non-asphyxiated infants, was 24.2 $\pm$ 0.9 years (95% confidence interval, CI = 23.9 - 24.5) versus 24.8 $\pm$ 0.7 years (95% CI = 26.4 - 25.0) $p<0.05$ respectively. The mean maternal parity was 2.9 $\pm$ 1.1 (95% CI = 2.5 - 3.3) for severely asphyxiated infants and 2.3 $\pm$ 1.4 (95% CI = 1.8 - 2.8) for non- asphyxiated infants $p>0.05$.

Comparing total duration of labour in mothers of infants with severe birth asphyxia and those whose infants did not have birth asphyxia, it was 8.2 $\pm$ 1.2 hours (95% CI = 7.8 - 8.6) versus 6.9 $\pm$ 0.8 hours (95% CI = 6.6 - 7.2); $p<0.01$. Further details on maternal characteristics are shown in Table I.

Table 2, total serum calcium concentrations at the ages of 12, 24 and 48 hours were significantly lower in asphyxiated neonates compared to non-asphyxiated neonates, with lowest value at age of 24 hours ($p<0.001$).

Asphyxiated neonates with normal mean serum calcium at the age of 12 hours tended to

maintain normal serum calcium concentration at the age of 48 hours (Table 3).

The mean total serum calcium concentration of the 9 asphyxiated neonates who received sodium bicarbonate therapy was significantly lower than that of their counterpart who did not receive bicarbonate therapy (Table 4).

The mean serum albumin levels were 35.6 g/L (range 34.8 – 51.5 g/L) and 35.8 g/L (range 36.1 – 52.6 g/L) in asphyxiated and non-asphyxiated neonates respectively. As shown in Table 5, the leading clinical manifestation associated with hypocalcaemia in infants with birth asphyxia was convulsion. Carpopedal spasm was not a prominent sign.

Table 1: Maternal characteristics of study infants

Maternal characteristics	Asphyxiated infants No (%)	Non-asphyxiated infants No (%)
Maternal age (years)		
< 20	3 (9.6)	2 (5.2)
20 – 34	20 (64.5)	31 (81.6)
≥ 35	6 (19.4)	5 (13.2)
Unknown	2 (6.5)	0 (0)
Total	**31 (100.0)**	**38 (100.0)**
Maternal parity		
0	8 (25.8)	4 (10.5)
1 – 4	17 (54.8)	23 (73.7)
≥ 5	6 (19.4)	5 (15.8)
Total	**31 (100.0)**	**38 (100.0)**
Mode of delivery		
Caesarean section	9 (29.0)	7 (18.4)
Vaginal	22 (71.0)	31 (81.6)
Total	**31 (100.0)**	**38 (100.0)**

Table 2: Mean total serum calcium concentration in asphyxiated and non-asphyxiated infants.

Age of infant	Mean total serum calcium in mmol/L		p-value
	Asphyxiated infants	Non-asphyxiated infants	
At 12 hours	1.80±0.06	2.08±0.07	< 0.001
At 24 hours	1.72±0.05	2.04±0.06	< 0.001
At 48 hours	1.74±0.05	2.07±0.06	< 0.001

Table 3: **Mean serum calcium concentrations in 24 asphyxiated neonates with normal values.**

Age of neonate	Mean Serum Calcium conc.
At 12 hours	1.85 ± 0.05 mmol/L
At 24 hours	1.82 ±0.05 mmol/L
At 48 hours	1.83 ± 0.05 mmol/L

Table 4: Comparison of mean serum calcium concentration (mmol/L) in neonates treated with bicarbonate and those without bicarbonate therapy.

Age of Neonates	Neonates with bicarbonate therapy (n = 9)	Neonates without bicarbonate therapy (n = 22)	p-value
At 12 hours	1.65 ± 0.04mmol/L	1.74 ±0.06 mmol/L	0.01
At 24 hours	1.65 ± 0.07mmol/L	1.73 ± 0.06 mmol/L	0.01
At 48 hours	1.70 ± 0.06mmol/L	1.78 ± 0.07 mmol/L	0.01

Table 5: Clinical manifestations in 7 infants with severe birth asphyxia and hypocalcaemia

Clinical manifestations	Asphyxiated hypocalcaemic infants(n=7)	Non-asphyxiated hypocalcaemic infants (n=3)
Convulsion	4.(57.1)	1 (33.3)
High-pitched cry	3 (42.9)	0 (0)
Twitching of extremities	3 (42.9)	0 (0)
Hypertonia	3 (42.9)	1 (33.3)
Jitteriness	2 (28.6)	2 (66.7)
Carpopedal spasm	1 (14.3)	3 (100.0)

Figures in parentheses are percentages. Some infants had more than one of these clinical manifestations.

DISCUSSION

In this study, the overall prevalence (22.6%) of early-onset neonatal hypocalcaemia among neonates with birth asphyxia was three times higher than that reported by Omene and Diejomaoh [12] among their asphyxiated neonates. Their lower prevalence may be accounted for by the retrospective nature of their study and the fact that serum calcium was not measured in all their study population. In this regard, some case records may be missing and some neonates with hypocalcaemia may also be missed, leading to the lower prevalence reported in that study.

Data from the present study showed that neonates with 1-minute Apgar scores of 3 or less had significantly lower mean total serum calcium concentration than their counterparts with 1-minute Apgar scores of 7 or more. Tsang et al [11] have reported similar findings. This implies that birth asphyxia plays a separate role in early neonatal calcium homeostasis.

In this study, asphyxiated neonates whose serum calcium concentrations were normal at the age of 12 hours tended maintain normal serum calcium at 48 hours of age. The clinical implication is that asphyxiated neonates whose total serum calcium at the age of 12 hours are normal are less likely to develop hypocalcaemia at the age of 48 hours.

Asphyxiated neonates who had sodium bicarbonate therapy during resuscitation tended to have significantly lower serum calcium concentration compared to their

counterparts who did not have sodium bicarbonate therapy. Similar finding has been reported by Tsang et al [11]. The adverse effect of bicarbonate therapy on serum calcium concentration reported in present study is reinforced by the reports of previous studies which concluded that bicarbonate administration during resuscitation is not only useless, but also, detrimental to the asphyxiated neonate [19,20]. Administration of sodium bicarbonate to correct acidosis is believed to be associated with movement of calcium from blood to bone, resulting in hypocalcaemia [21].

In this study, the leading sign associated with hypocalcaemia in asphyxiated neonates was convulsion. It is worthy of note that carpopedal spasm was not a prominent physical sign among the hypocalcaemic neonates who suffered birth asphyxia.

Some limitations of the present study must be considered. Firstly, the use of Apgar score in defining birth asphyxia. The Apgar Scoring System, [22] though very useful in the measurement of birth asphyxia, has its shortcomings in that it does not fully define birth asphyxia [23,24]. It is known that factors (maternal medication) other than asphyxia may affect the Apgar score of an infant. However, in the review by Addy [27] he noted that Apgar score was the basis of many papers on the outcome of birth asphyxia, justifying its use in the present study. Secondly, our inability to measure directly ionized serum calcium concentration and blood gases. This was due to lack of facility for their determination in our hospital. Future study will take this into consideration. Despite these limitations, the study gave an insight into the prevalence of the early-onset neonatal hypocalcaemia.

In conclusion, hypocalcaemia was common among asphyxiated neonates, particularly if they received bicarbonate therapy during resuscitation. Asphyxiated neonates whose serum calcium concentration was normal at the age of 12 hours tended to maintain this normocalcaemia at the age of 48 hours.

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