

Prevalence and Clinical Profile of Hypocalcemia in Term Neonates Hospitalized With Birth Asphyxia

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Abstract

Background : Hypocalcemia is a commonly observed abnormality in neonates with birth asphyxia. In healthy term infants, serum calcium reaches a physiological nadir of 7.5-8.5 mg/dL by 24-48 hours of age. It is during this phase of nadir that serum calcium may drop to hypocalcemic levels in high-risk neonates, like infants of diabetic mothers, neonates with birth asphyxia and preterm infants. In neonates with birth asphyxia, factors like delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, renal insufficiency and diminished parathyroid hormone secretion may contribute to hypocalcemia. Routine screening for hypocalcemia is recommended at 24 and 48 hours of age in high-risk neonates.

Aims and objectives: To estimate the prevalence of hypocalcaemia in term neonates hospitalized with birth asphyxia and determine its clinical profile and short-term outcome.

Materials and Methods: A prospective longitudinal study was carried out in Paediatric Department, RIMS, Imphal during a period of two years (Aug. 2018 - July 2020). 236 term neonates admitted with birth asphyxia were enrolled. The patients' information, details of case history and relevant examination, laboratory investigations, treatment received, duration of admission and final diagnosis at the time of discharge/death were recorded in a pre-designed patient's case record form. Venous blood (1 mL) was collected and sent immediately to Biochemistry Department, RIMS, Imphal for total serum calcium level estimation. Hypocalcemia was defined as total serum calcium <8 mg/dL (2 mmol/L). The participants were further followed up till 6 months of age to look for any neurological sequelae.

Result : Hypocalcemia with total serum calcium <8 mg/dL was documented in 41 (17.4%) out of 236 term neonates hospitalized with perinatal asphyxia. Statistically significant associations were found between hypocalcemia and severe birth asphyxia (Apgar score 0-3), maternal diabetes, formula feeding and positive pressure ventilation (PPV). A large proportion (82.9%) of neonates with hypocalcaemia were symptomatic - seizure being the most common symptom (35.2%), followed by jitteriness (20.5%), poor feeding (17.6%), lethargy, irritability and high pitch cry (8.8%) each.

Conclusion : Birth asphyxia is a significant risk factor for hypocalcaemia. The other risk factors noted were infants of diabetic mothers, formula feeding, neonates receiving bag and mask ventilation. Seizure was found to be most common symptom. Hypocalcaemia should be anticipated in neonates with birth asphyxia, and a timed intervention is required, thereby preventing its complications.

Keywords: Birth asphyxia, hypocalcaemia, term neonate.

Date of Submission: 18-03-2022

Date of Acceptance: 02-04-2022

I. Introduction

The World Health Organization (WHO) defines birth asphyxia (also known as perinatal asphyxia or neonatal asphyxia) as "failure to initiate sustained breathing at birth."¹ As per the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG), all of the following must be present for designation of perinatal asphyxia (a) profound metabolic or mixed acidemia (pH<7) in umbilical cord blood; (b) persistence of Apgar scores less than 3 for longer than 5 minutes; (c) neonatal neurological sequelae (e.g. seizures, encephalopathy, tone abnormalities); (d) multiple organ involvement (kidney, lungs,

liver, heart, intestine).² According to WHO, 4 million deaths per year occur due to birth asphyxia, which is one of the most common causes of under-5 mortality (8.5%).³ Among the neonatal mortality, 23% of all deaths are caused by birth asphyxia.⁴

Hypocalcemia is a commonly observed clinical or laboratory abnormality in neonates with birth asphyxia. During pregnancy, calcium is actively transferred from mother to fetus mostly in the third trimester.⁵ A positive calcium balance is maintained across the placenta by the parathyroid hormone-related peptide (PTHrP). Calcitonin and parathyroid hormone (PTH) do not cross the placenta. At term, fetal serum calcium is 10-11 mg/dL, which is 1-2 mg/dL higher than the maternal value.⁶

After birth, serum calcium levels depend on the PTH secretion in the newborn, calcium intake, vitamin D status, skeletal calcium stores and reabsorption of calcium in the kidneys.⁶ In healthy term infants, serum calcium reaches a physiological nadir of 7.5-8.5 mg/dL by 24-48 hours of age and is related to abnormalities in vitamin D metabolism, hypoparathyroidism, reduced response to PTH in the end-organs, hyperphosphatemia, hypomagnesemia and hypercalcitonemia.^{7,8} PTH level eventually rises during the first 48 hours of life in otherwise healthy term neonates and normal calcium levels are attained by day 3 of life.^{6,9} It is during this phase that serum calcium may drop to hypocalcemic levels in high-risk neonates, like infants of diabetic mother, neonates with birth asphyxia and preterm infants.⁶

Hypocalcemia in term neonates is defined as total serum calcium <8 mg/dL (2 mmol/L), or ionic calcium <4.8 mg/dL (1.2 mmol/L); corresponding cut-off values in preterm neonates are <7 mg/dL (1.75 mmol/L) and <4 mg/dL (1 mmol/L), respectively.^{6,10} In perinatal asphyxia delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, renal insufficiency, and diminished parathyroid hormone secretion may contribute to hypocalcemia.⁶

Routine screening for hypocalcemia is recommended at 24 and 48 hours of age in high-risk neonates.⁶

- a) Neonates with severe birth asphyxia (Apgar score <4 at 1 minute of age);
- b) Preterm neonates with period of gestation (POG) <32 weeks;
- c) Infants of diabetic mothers on intravenous (IV) fluids.

Currently, prophylactic administration of 40 mg/kg/day of elemental calcium (4 mL/kg/day of 10% calcium gluconate) is recommended in high-risk group of infants: neonates with severe birth asphyxia, preterm babies (<32 weeks POG) and sick infants of diabetic mothers.⁶ However, there is paucity of data and no sufficient evidence to support this practice. Hence, this study was conducted to estimate the prevalence of hypocalcemia in term neonates with perinatal asphyxia and to determine its clinical predictors.

Aim and objectives: To estimate the prevalence of hypocalcemia in term neonates with birth asphyxia and determine its clinical profile and short-term outcome.

II. Material And Methods

Prospective longitudinal study carried out in Paediatric Department, RIMS, Imphal during a period of two years (August 2018-July 2020)

Study design: A hospital based prospective longitudinal study

Study setting: Department of Paediatrics, RIMS, Imphal

Study duration: 2 years (August 2018-July 2020)

Study population: All term neonates with POG 37+0/7 weeks to 41+6/7 weeks with birth asphyxia admitted in the Paediatric ward, RIMS Hospital, Imphal during the study period fulfilling the inclusion and exclusion criteria.

Inclusion criteria:

A term neonate with any one of the following criteria:

1. Documentation of intrapartum fetal distress through recognition of abnormal fetal heart rate patterns with or without passage of meconium.
2. Presence of immediate neonatal distress as evidenced by Apgar score <7 at 1 minute of age.
3. Need for immediate neonatal resuscitation including bag and mask ventilation.
4. An abnormal neurologic examination during the first 24 hours of life as judged by application of Sarnat and Sarnat staging.¹¹

Exclusion Criteria:

1. All neonates with evidence of intrauterine infection and severe congenital anomalies
2. Parents or legal guardians refusing consent

Sample size: Using estimated prevalence (P) of hypocalcemia in term neonates with perinatal asphyxia as 21.1% according to a prior study done by Azam H et al.,¹² sample size was calculated as 236.

Patient details and laboratory measurements: Patient's information, details of case history and relevant examination, laboratory investigations, treatment received, duration of admission and final diagnosis were recorded in a pre-designed patient's case record form. For asymptomatic neonates, screening for hypocalcemia was done at 24 hours and 48 hours of life.⁶ Symptomatic newborns were evaluated at the time of clinical presentation (jitteriness, exaggerated startle, myoclonic jerks, seizures and non-specific symptoms like poor feeding, lethargy, irritability, high-pitched cry etc.). Venous blood (1 mL) was collected and sent immediately to Biochemistry Department, RIMS, Imphal for total serum calcium level. As our study included only term infants, hypocalcemia was defined as total serum calcium <8 mg/dL (2 mmol/L).^{6,10} The participants were further followed up till 6 months of age to look for any neurological sequelae.

Statistical analysis: The data and findings of the study were entered into a personal computer, using SPSS (IBM) for Windows (Version 21.0). Prevalence of hypocalcemia in term neonates hospitalized with birth asphyxia was calculated. Differences in proportions (for categorical data) and those in means (for continuous data) were calculated using Chi square test and Student t-test, respectively. $P < 0.05$ was considered significant.

Ethical issues:

Clearance was obtained from the Research Ethics Board, RIMS, Imphal. A written informed consent for enrolment in the study was obtained from the parents/guardians/care-givers of the neonates.

III. Results

Hypocalcemia with total serum calcium <8 mg/dL was documented in 41 (17.4%) out of 236 term neonates hospitalized with perinatal asphyxia, as depicted in **Table I**. Among the enrolled participants, 143 (60.6%) were males.

Table I Total Serum Calcium Distribution among Term neonates admitted with perinatal asphyxia(n=236)

Total Serum Calcium (mg/dL)	Frequency N (%)
≥ 8	195 (82.6)
< 8	41 (17.4)
Total	236

Out of 236 neonates enrolled, 125 (53%) and 65 (27.5%) infants had Apgar scores between 4-6 and >6 at 1 minute of age, respectively and 46 (19.5%) had severe birth asphyxia (<4 Apgar score at 1 minute of age). A majority of the neonates (n=183, 77.5%) received positive pressure ventilation (PPV). Twenty (8.5%) infants hospitalized with perinatal asphyxia were born to mothers with diabetes. Association between different clinical parameters and hypocalcemia is depicted in **Table II**.

Table II Association between different clinical parameters and hypocalcemia in term neonates with birth asphyxia (n=236)

Parameters	No. of neonates N	No. of neonates with hypocalcemia N(%)	p-value
Male	143	23 (56.1)	0.598
Female	93	18 (43.9)	
APGAR score ≤3	46	24 (52.2)	0.001
APGAR score >3	190	17 (8.9)	
PPV [*]	183	37 (20.2)	0.038
No PPV	53	4 (7.5)	
Infant of diabetic mother	20	12 (60)	0.001
No h/o maternal diabetes	216	29 (13.4)	
Formula feeding	39	22 (56.4)	0.001
Exclusive breast-feeding	197	19 (9.6)	
Maternal use of AED [#]	2	1 (50)	0.318
No h/o AED use in mother	234	40 (17.1)	

* PPV= Positive pressure ventilation; [#]AED= Anti-epileptic drug

Twenty-four (52.2%) out of 46 infants with severe birth asphyxia had hypocalcemia. Among neonates with APGAR scores 4-6 and >6, 13 (11.6%) and 4 (6.5%) infants had hypocalcemia, respectively. These findings were found to be statistically significant ($P=0.001$) showing association between severe birth asphyxia and hypocalcaemia.

Out of 183 neonates who received PPV, 37 (20.2%) had hypocalcemia while 4 (7.5%) out of 53 neonates who did not receive PPV developed hypocalcemia. This showed a statistically significant association between hypocalcemia and PPV ($P=0.038$).

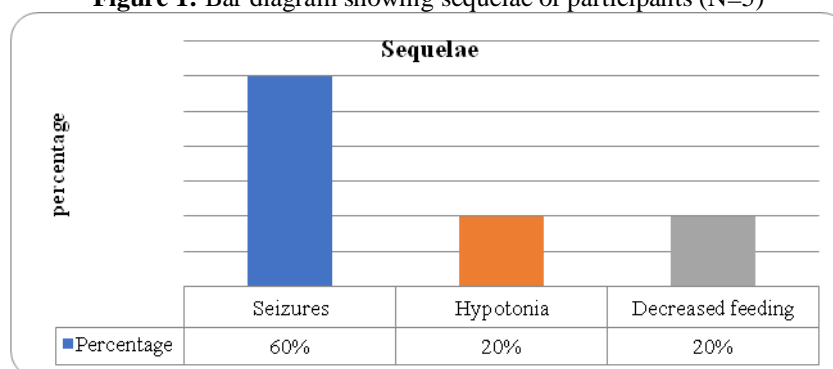
Twelve (60%) out of 20 infants born to diabetic mothers developed hypocalcemia. Among 216 neonates with no history of maternal diabetes, 29 (13.4%) had hypocalcemia. The difference between the two groups was statistically significant ($P=0.001$).

Neonates with birth asphyxia on formula feeding were found hypocalcemic (56.4%) than those neonates fed with mother milk (9.6%) ($P<0.05$).

Out of 41 hypocalcemic infants, 34 (83%) of them developed symptoms. Seizure was found to be the most common symptom constituting 35.2% followed by jitteriness (20.5%), poor feeding (17.6%), and lethargy, irritability and high pitch cry, each constituting 8.8%.

Majority (64.7%) of the neonates with hypocalcaemia recovered without sequelae. **Figure – 1** shows that among neonates who developed sequelae, 60% of them developed seizures on follow-up till 6 months of age.

Figure 1: Bar diagram showing sequelae of participants (N=5)



IV. Discussion

The prevalence of hypocalcemia in term neonates with asphyxia was found to be 17.4%, which is lower than the results found in various prospective studies conducted before, such as the study done by Onyiriuka AN¹³ who reported an overall prevalence of 22.6% early-onset neonatal hypocalcaemia among asphyxiated neonates with Apgar score of 3 or less than 3.¹³ This difference could be because the study conducted by Onyiriuka AN included only infants with severe birth asphyxia. Hypocalcemia in asphyxiated neonates may be due to increased phosphate load due to cellular damage, increased calcitonin production and decreased PTH production.^{6,14,15} Among neonates having APGAR score 0-3, a majority (52.2%) of them developed hypocalcaemia, in contrast to those with higher APGAR scores (4 - 6, and >6). These findings were found to be statistically significant ($P<0.05$) showing association between birth asphyxia and hypocalcaemia in neonates.

No significant ($P>0.05$) association could be established between sex and serum Calcium. This finding is similar to study conducted by Khalesi N *et al.*¹⁴ However, a statistically significant association could be established between diabetes in mother and hypocalcaemia in neonates ($P<0.05$). This finding is supported by study conducted by Azam H *et al.*¹² Infants of diabetic mothers (IDMs) show an exaggerated postnatal drop in circulating calcium levels with hyperphosphatemia between 24 and 72 hours after birth. Greater bone mass and relative undermineralization typical of macrosomic IDMs may increase the neonatal demand for calcium, producing a deeper and prolonged decline in postnatal serum calcium levels. In addition, magnesium deficiency in these infants can lead to decreased PTH production and action.¹⁵

A significant ($p < 0.05$) association is observed between type of feeding and serum calcium. Neonates with birth asphyxia on formula feeding were found hypocalcemic (56.4%) than those neonates fed with mother milk (9.6%). These findings were similar to the result of study conducted by Yadav P *et al.*¹⁶

A large proportion (82.9%) of neonates with hypocalcaemia was symptomatic in our study. This is in contrary to the study done by Jain BK *et al.*¹⁷ in which only 48% of hypocalcaemic infants were symptomatic. The higher

incidence of symptomatic infants in our study may be because of other factors such as infants of diabetic mothers, formula feeding which were taken into consideration in our study.

Seizure was found to be the most common sign/symptom constituting 35.2%, followed by jitteriness (20.5%), poor feeding (17.6%), lethargy, irritability and high pitch cry (8.8%) each. This was similar to the study conducted by Onyiriuka AN who also reported that the commonest clinical finding among asphyxiated neonates with early-onset hypocalcaemia was convulsions (57.1%).¹³

Most (64.7%) of the neonates with hypocalcaemia recovered without sequelae. In those neonates who developed sequelae, majority (60%) had seizures on follow up. But this may be also related to birth asphyxia.

V. Conclusion

Birth asphyxia is a significant risk factor for hypocalcaemia. The other risk factors noted were infant of diabetic mothers, formula feeding, neonates receiving bag and mask ventilation. Seizure was found most common sign/symptoms. Hypocalcaemia should be anticipated in neonates with birth asphyxia, and a timed intervention is required, thereby preventing the complications.

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Dr. Deepak Sharma, et. al. "Prevalence and Clinical Profile of Hypocalcemia in Term Neonates Hospitalized With Birth Asphyxia." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(03), 2022, pp.50-54.