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Early Onset Hypocalcaemia in Sick Newborns: A Prospective Observational Study

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Abstract

Introduction: Calcium physiology is in transitional state after birth and may be deranged by various neonatal disorders leading to hypocalcaemia. Coexisting hypocalcaemia can further worsen underlying condition and increase mortality. This prospective observational study was done to study the incidence, clinical correlates and outcome of early onset hypocalcaemia in sick newborns.

Methods: A prospective observational study was done on 175 sick newborns. Ionized serum calcium levels were measured at six, 24, 48 and 72 hours of age by arterial blood gas analyzer. Maternal and neonatal characteristics, ionized calcium levels, clinical course and outcomes were recorded. Patient characteristics and neonatal morbidities were compared between hypercalcaemic group and normocalcaemic group by chi square test. Odds ratio was calculated to see correlation between hypocalcaemia with respiratory support and death.

Results: Early onset hypocalcaemia occurred in 101 of 175 (57.7%) sick newborns. Early onset hypocalcaemia was higher in preterm babies (59.7%) than term babies (54.1%). Meconium stained amniotic fluid, obstructed labour and MAS were significantly associated with early onset hypocalcaemia. Newborns with MAS and HIE had high incidence of hypocalcaemia in both term and preterm groups. Newborns with hypocalcaemia were more likely to receive mechanical ventilation (OR 2.84; CI 1.28-6.30; p value 0.01) and had higher mortality (OR 2.10; CI 1.02-4.33; p value 0.04).

Conclusions: Early onset hypocalcaemia is very common in sick newborns. Meconium aspiration syndrome was a significant risk factor for early onset hypocalcaemia. Early onset hypocalcaemia was associated with higher odds of receipt of mechanical ventilation and mortality.

Introduction

Calcium is essential for many biochemical processes in our body including blood coagulation, neuromuscular excitability, cell membrane integrity, gene transcription, cell differentiation, bone mineralization and many of the cellular enzymatic activities.[1-3] About 99% of body calcium is present in the bone tissue and the remaining is present in the extracellular fluid.[2] Ionized calcium is the active form of calcium and comprises about half of calcium present in the extracellular fluid.[4] During the last trimester, calcium is actively transferred from mother to the foetus as revealed by significantly higher total calcium concentrations in cord blood compared to maternal serum.[5] After birth, calcium levels decline and reach a nadir in healthy term babies by 24 to 48 hours of age, followed by gradual increase.[6,7] The nadir may approach hyper calcaemic levels in sick neonates, leading to undesirable consequences due to essentiality of calcium in

many cellular and biochemical processes.

Early onset hypocalcaemia occurs in first 72 hours of life while late onset hypocalcaemia presents after 72 hours of life and usually by the end of first week of life. The symptoms of early onset hypocalcaemia are more subtle than late onset hypocalcaemia so identification is difficult without routine screening in sick newborns. Prematurity, infant of diabetic mother, perinatal asphyxia and maternal hyperparathyroidism are some of the risk factors for early onset hypocalcaemia.[8,9]

Calcium physiology is in transition after birth, and it may be easily deranged by various neonatal disorders. Hypocalcaemia is one of the common metabolic abnormalities in newborn period. A sick newborn is in a state of physiologic compromise which can be further aggravated by co-existing hypocalcaemia, with undesirable consequences. Calcium homeostasis may be influenced by neonatal care practices, such as alkali therapy,[10-12] which has become less frequent now than in past. However, there is scarcity of information on early onset hypocalcaemia in current era. This prospective observational study aimed to analyse the incidence, clinical correlates and outcome of early onset hypocalcaemia in contemporary cohort of sick newborns admitted to a Level III Neonatal Intensive Care Unit (NICU) of a tertiary care teaching hospital.

Methods

We prospectively studied 175 sick newborns admitted over a period of six months from December 2018 to May 2019. Early onset hypocalcaemia was defined as ionized serum calcium level below 1 mmol / l within 72 hours of age.[8,9] Ionized calcium levels were measured at six, 24, 48 and 72 hours of age using arterial blood gas analyser. Study cohort included all sick neonates admitted to NICU who required frequent blood gas monitoring for their care. Neonates with the following conditions were included in the study: post-resuscitation care, hypoxic ischemic encephalopathy (HIE), meconium aspiration syndrome (MAS), early onset sepsis (EOS), respiratory distress syndrome (RDS), seizures, transient tachypnoea of newborn (TTN) and polycythaemia. Newborns with major congenital malformations, hyperbilirubinemia requiring phototherapy and minor problems were excluded. Maternal and neonatal characteristics, ionized calcium levels, clinical course and outcomes were recorded. Based on ionized calcium levels neonates were divided into neonates with hypocalcaemia and neonates with normocalcaemia. The neonatal and maternal characteristics and neonatal morbidities were compared between these two groups by chi square test. Odds ratio was calculated to see significant correlation between hypocalcaemia with respiratory support type and death. The diagnosis of EOS, HIE, post resuscitation care, MAS, RDS and TTN were made on the basis of clinical, laboratory and radiological criteria. Ethical clearance was taken from Institute Ethical Committee. Informed consent was taken from parents. We used chi square and Fisher's exact test for categorical data and p value < .05 was taken as significant. For comparing medians, we used median test.

Results

Study population included 175 sick newborns of which 101 (57.7%) showed early onset hypocalcaemia. Hypocalcaemia occurred in 68 (59.7%) of 114 preterm newborns and in 33 (54.1%) of 61 term newborns and the difference was not significant statistically (p value 0.58).

Table 1. Maternal and neonatal characteristics of study population. IQR - Interquartile range; LSCS - Lower segment caesarean section; PPROM - Preterm premature rupture of membrane; PIH - Pregnancy induced hypertension; MSAF - Meconium stained amniotic fluid; HBsAg - Hepatitis B surface antigen; AGA-Appropriate for gestational age; SGA - Small for gestational age; LGA - Large for gestational age

	Hypocalcaemia (n = 101)	Normocalcaemia (n = 74)	P value
Maternal characteristics			
Gravida, median (IQR)	2 (1-3)	2 (1-3)	0.273
Parity, median (IQR)	1 (0-1)	1 (0-1.5)	0.62
Spontaneous vaginal delivery, n (%)	31 (30.7%)	22 (29.7%)	1
LSCS, n(%)	70 (69.3%)	52 (70.3%)	
PPROM, n (%)	30 (29.7%)	20 (27.0%)	0.823
Eclampsia/preeclampsia/PIH, n (%)	18 (17.8%)	16 (21.6%)	0.664
MSAF, n (%)	25 (24.8%)	7 (9.5%)	0.017
Placenta previa, n (%)	4 (4.0%)	3 (4.1%)	1
Maternal diabetes, n (%)	2 (2%)	2 (2.7%)	1
Oligohydramnios, n (%)	5 (5.0%)	3 (4.1%)	1
Polyhydramnios, n (%)	2 (2.0%)	1 (1.4%)	1
Obstructed labour, n (%)	9 (8.9%)	1 (1.4%)	0.046
Ruptured uterus, n (%)	1 (1.0%)	2 (2.7%)	0.574
Maternal heart disease, n (%)	1 (1.0%)	3 (4.1%)	0.312
Maternal hypothyroidism, n (%)	4 (4.0%)	3 (4.1%)	1
HBsAg positive, n (%)	2 (2.0%)	2 (2.7%)	1
Twin pregnancy, n (%)	8 (7.9%)	7 (9.4%)	0.932
Severe anemia, n (%)	2 (2.0%)	1 (1.4%)	1
Cord around neck, n (%)	1 (1.0%)	0 (0%)	1
Neonatal characteristics			
Male, n (%)	61 (60.4%)	46 (62.2%)	0.936
Female, n (%)	40 (39.6%)	28 (37.8%)	
Gestational age (wk), median (IQR)	35 (31.3-37.7)	35.8 (31.4-37.7)	0.83
Birth weight (g), median (IQR)	2050 (1420-2682.5)	1810 (1337.5-2500)	0.48
Gestation, n (%)			0.583
Term	33 (32.7%)	28 (37.8%)	
Preterm	68 (67.3%)	46 (62.2%)	

Meconium stained amniotic fluid (MSAF) and obstructed labour were observed more frequently in newborns with hypocalcaemia. Neonatal characteristics such as gender, gestational age and birth weight were comparable between two groups.

Table 2. Incidence of early onset hypocalcemia in different neonatal morbidities in term and preterm newborns. HIE - Hypoxic ischemic encephalopathy; MAS - Meconium aspiration syndrome; EOS - Early onset sepsis; TTN - Transient tachypnoea of newborn; RDS - Respiratory distress syndrome

Morbidities	Total cases	Hypocalcaemia n (%)	Normocalcaemia n (%)	P value
Term (37 wk)	N = 61	N = 33	N = 28	
Post resuscitation care	12	5 (41.7%)	7 (58.3%)	0.52
HIE	12	7 (58.3%)	5 (41.7%)	0.99
MAS	13	11 (84.6%)	2 (15.4%)	0.03
EOS	7	2 (28.6%)	5 (71.4%)	0.30
Seizure	1	1 (100%)	0 (0%)	1
TTN	14	6 (42.9%)	8 (57.1%)	0.51
Polycythaemia	2	1 (50%)	1 (50%)	0.55
Preterm (< 37wk)	N = 114	N = 68	N = 46	
RDS	48	28 (58.3%)	20 (41.7%)	0.96
Post resuscitation care	27	14 (51.9%)	13 (48.1%)	0.47
EOS	24	13 (54.2%)	11 (45.8%)	0.70
HIE	5	4 (80%)	1 (20%)	0.63
Seizure	2	2 (100%)	0 (0%)	0.51
MAS	5	5 (100%)	0 (0%)	0.08
Polycythaemia	3	2 (66.7%)	1 (33.3%)	0.73

Table 2 shows incidence of early onset hypocalcaemia in different neonatal morbidities. Eleven of 13 term newborns with MAS had hypocalcaemia which is significantly higher (p value = 0.03) compared to other morbidities. MAS and HIE had high incidence of hypocalcaemia in both term and preterm neonates. None of the newborns received alkali therapy or blood transfusion during first three days of age. None of the mothers received anticonvulsants and diuretics which could have influenced serum calcium levels in newborns. We do not administer prophylactic calcium to sick newborns in our set up. Calcium is administered only in newborns with documented hypocalcaemia.

Table 3. Respiratory support and outcome in early onset hypocalcaemia.

	Total cases	Hypocalcaemia	Normocalcaemia			P value
Respiratory support type						
Mechanical ventilation	59	40 (67.80%)	19 (32.20%)	2.84	(1.28 - 6.30)	0.01
Non invasive respiratory support	69	41 (59.42%)	28 (40.58%)	1.98	(0.93 - 4.19)	0.08
No support	47	20 (42.55%)		ref		
Outcome						
Death	46	32 (69.57%)	14 (30.43%)	2.10	(1.02 - 4.33)	0.04
LAMA	8	6 (75%)	2 (25%)	2.76	(0.54-14.23)	0.22
Discharged	121	63 (52.07%)	58 (47.93%)	ref		

LAMA - Left against medical advice

Table 3 shows the relationship between respiratory support and outcome and early onset hypocalcaemia. Newborns with hypocalcaemia were more likely to receive mechanical ventilation (odds ratio 2.84; confidence interval 1.28-6.30; p value 0.01) and experienced increased mortality (odds ratio 2.10; confidence interval 1.02-4.33; p value 0.04).

Discussion

The present study revealed a high incidence of hypocalcaemia in sick newborns during first three days age. Hypocalcaemia was observed in 57.7% of study cohort. Calcium is essential for numerous physiological processes.[1-3] Co-existing hypocalcaemia can worsen physiological instability in a sick newborn. The clinical signs of hypocalcaemia are usually nonspecific but can contribute to some serious problems like apnoea, seizures and abnormalities in cardiac functions. As the manifestation of hypocalcaemia are non-specific, categorizing these problems as primarily due to hypocalcemia is often difficult, more so in sick neonates. Therefore, it is important to frequently monitor and correct low serum calcium levels in sick newborns to optimize their care and outcome. In a study by Roberton et al on 131 ill newborns, 51 infants developed hypocalcaemia before 96 hours of age, and 45 of these were hypocalcemic before 48 hours of age.[10]

In our study meconium stained amniotic fluid, obstructed labour and MAS were significantly associated with early onset hypocalcaemia. The incidence of early onset hypocalcaemia was high in both term and preterm neonates with HIE and MAS. Previous studies had shown that neonates with perinatal asphyxia had significantly lower mean calcium level compared to the controls.[13-15] Basu et al. found that hypocalcaemia together with hyponatremia occurred early in the newborns with perinatal asphyxia and decrease in their serum levels was directly proportional to each other and to the degree of asphyxia.[13] Fetal hypoxic stress can stimulate colonic activity, resulting in the passage of meconium and also stimulates foetal gasping movements that result in meconium aspiration in utero.[16] Evidence suggests chronic in utero insult may be responsible for most cases of severe MAS as opposed to an acute peripartum event.[17-19] The main causes of hypocalcaemia in infants with asphyxia include increased phosphate load due to cellular damage, increased calcitonin production, renal failure, and functional hypoparathyroidism.[11,20]

We observed higher incidence of hypocalcaemia in preterm newborns than in term newborns although the difference was not statistically significant. This suggests increased vulnerability of preterm population to hypocalcaemia and its consequences. Previous study by Venkataraman et al had shown the high incidence of early onset hypocalcaemia refractory to high doses of calcitriol in infants born at or before 32 weeks of gestation.[21] The causes of hypocalcaemia in premature infants include early discontinuation of calcium transfer through the placenta, functionally immature or suppressed parathyroids, reduced response of target organs to PTH, and increased calcitonin levels.[20,22]
Neonatal care practices may influence serum calcium levels, particularly ionized calcium levels. Bicarbonate administration may cause significant decrease in calcium ion activity, whereas total calcium concentration remains unchanged.[12]

During exchange transfusion with acid citrate dextrose (ACD) - Tham buffered blood, calcium ion activity decreased significantly, whereas total calcium levels were found to be increased because of the routine administration of calcium gluconate.[12] In present era the use of intravenous sodium bicarbonate for correction of metabolic acidosis has become controversial due to lack of evidence of its benefits and growing evidence of its harmful effects. Several studies showed significant side effects of sodium bicarbonate infusions, such as fluctuations in cerebral and cardiovascular hemodynamic, increased risk of severe intraventricular haemorrhage (IVH) and mortality.[23-25] In current practice alkali therapy is not recommended during delivery room resuscitation.[26] We rarely use bicarbonate therapy in our unit. None of the patients included in the study received bicarbonate or blood transfusion.

There is correlation between severity of illness with hypocalcaemia in the first few days of life.[10] There may be significant differences in levels of ionized calcium, magnesium, and phosphate in neonates with sepsis as compared to neonates without sepsis.[27] These authors found significant association of hypocalcaemia with organ dysfunction and sepsis-related mortality. The present study found higher rates of hypocalcaemia in neonates who died compared to those who survived. This could be explained by the essentiality of calcium in various biochemical and cellular processes which could be adversely affected in the presence of hypocalcaemia in a sick baby.

Maternal vitamin D deficiency may be associated with early neonatal hypocalcaemia in preterm newborns, but not in term infants.[28] A study from India concluded that maternal vitamin D deficiency is a major cause of hypocalcaemic seizures in infants below six months of age.[29] Maternal hyperparathyroidism is also a risk factor for early onset hypocalcaemia in newborn.[30] We did not assess maternal vitamin D and parathyroid hormone levels and this was the major limitation of our study.

Conclusions

There is high incidence of early onset hypocalcaemia in sick newborns. Meconium stained amniotic fluid, obstructed labour and MAS were found to be the major risk factors for early onset hypocalcaemia. Early onset hypocalcaemia was associated with increased need for mechanical ventilation and death. This study shows the importance of strict monitoring of ionized calcium levels in the first 72 hours of life in sick newborns.

References

1. Campbell AK. Calcium as an intracellular regulator. Proc Nutr Soc. 1990 Feb;49(1):51-6.
DOI: 10.1079/pns19900008.

2. Beto JA. The role of calcium in human aging. Clin Nutr Res. 2015 Jan;4(1):1-8.
DOI: 10.7762/cnr.2015.4.1.1. Epub 2015 Jan 16.

3. Bootman MD, Collins TJ, Peppiatt CM, Prothero LS, MacKenzie L, De Smet P, et al. Calcium signalling–an overview. Semin Cell Dev Biol. 2001 Feb;12(1):3-10. DOI: 10.1006/scdb.2000.0211.

4. Robertson WG, Marshall RW. Calcium measurements in serum and plasma–total and ionized. CRC Crit Rev Clin Lab Sci. 1979 Dec;11(3):271-304. DOI: 10.3109/10408367909105859.

5. Schauberger CW, Pitkin RM. Maternal-perinatal calcium relationships. Obstet Gynecol. 1979 Jan;53(1):74-6. PMID: 760023.

6. David L, Anast CS. Calcium metabolism in newborn infants. The interrelationship of parathyroid function and calcium, magnesium, and phosphorus metabolism in normal, "sick," and hypocalcemic newborns. J Clin Invest. 1974 Aug;54(2):287-96. DOI: 10.1172/JCI107764.

7. Hillman LS, Rojanasathit S, Slatopolsky E, Haddad JG. Serial measurements of serum calcium, magnesium, parathyroid hormone, calcitonin, and 25-hydroxy-vitamin D in premature and term infants during the first week of life. Pediatr Res. 1977 Jun;11(6):739-44. DOI: 10.1203/00006450-197706000-00009.

8. Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcemia in the newborn. Indian J Pediatr. 2010 Oct;77(10):1123-8. DOI: 10.1007/s12098-010-0176-0. Epub 2010 Aug 25.

9. Vuralli D. Clinical Approach to Hypocalcemia in Newborn Period and Infancy: Who Should Be Treated? Int J Pediatr. 2019 Jun 19;2019:4318075. DOI: 10.1155/2019/4318075.

10. Roberton NR, Smith MA. Early neonatal hypocalcaemia. Arch Dis Child. 1975 Aug;50(8):604-9. DOI: 10.1136/adc.50.8.604.

11. Tsang RC, Chen I, Hayes W, Atkinson W, Atherton H, Edwards N. Neonatal hypocalcemia in infants with birth asphyxia. J Pediatr. 1974 Mar;84(3):428-33. DOI: 10.1016/s0022-3476(74)80733-x.

12. Radde IC, Parkinson DK, Höffken B, Appiah KE, Hanley WB. Calcium ion activity in the sick neonate: effect of bicarbonate administration and exchange transfusion. Pediatr Res. 1972 Jan;6(1):43-9. DOI: 10.1203/00006450-197201000-00007.

13. Basu P, Som S, Das H, Choudhuri N. Electrolyte status in birth asphyxia. Indian J Pediatr. 2010 Mar;77(3):259-62. DOI: 10.1007/s12098-010-0034-0. Epub 2010 Feb 22.

14. Odo KE, Odetunde OI, Chinawa JM, Okafor HU, Aronu AE, Adimora GN. Comparison of plasma electrolytes of perinatally asphyxiated and normal term babies. J Neonatal Perinatal Med. 2019;12(4):385-9. DOI: 10.3233/NPM-1839.

15. Jajoo D, Kumar A, Shankar R, Bhargava V. Effect of birth asphyxia on serum calcium levels in neonates. Indian J Pediatr. 1995 Jul-Aug;62(4):455-9. DOI: 10.1007/BF02755067.

16. Swarnam K, Soraisham AS, Sivanandan S. Advances in the management of meconium aspiration syndrome. Int J Pediatr. 2012;7:357. DOI: 10.1155/2012/359571.

17. Ghidini A, Spong CY. Severe meconium aspiration syndrome is not caused by aspiration of meconium. Am J Obstet Gynecol. 2001 Oct;185(4):931-8. DOI: 10.1067/mob.2001.116828.

18. Rossi EM, Philipson EH, Williams TG, Kalhan SC. Meconium aspiration syndrome: intrapartum and neonatal attributes. Am J Obstet Gynecol. 1989 Nov;161(5):1106-10. DOI: 10.1016/0002-9378(89)90643-1.

19. Richey SD, Ramin SM, Bawdon RE, Roberts SW, Dax J, Roberts J, et al. Markers of acute and chronic asphyxia in infants with meconium-stained amniotic fluid. Am J Obstet Gynecol. 1995 Apr;172(4 Pt 1):1212-5. DOI: 10.1016/0002-9378(95)91481-1.

20. Venkataraman PS, Tsang RC, Chen IW, Sperling MA. Pathogenesis of early neonatal hypocalcemia: studies of serum calcitonin, gastrin, and plasma glucagon. J Pediatr. 1987 Apr;110(4):599-603. DOI: 10.1016/s0022-3476(87)80560-7.

21. Venkataraman PS, Tsang RC, Steichen JJ, Grey I, Neylan M, Fleischman AR. Early neonatal hypocalcemia in extremely preterm infants. High incidence, early onset, and refractoriness to supraphysiologic doses of calcitriol. Am J Dis Child. 1986 Oct;140(10):1004-8. DOI: 10.1001/archpedi.1986.02140240050025.

22. Tsang RC, Light IJ, Sutherland JM, Kleinman LI. Possible pathogenetic factors in neonatal hypocalcemia of prematurity. The role of gestation, hyperphosphatemia, hypomagnesemia, urinary calcium loss, and parathormone responsiveness. J Pediatr. 1973 Mar;82(3):423-9. DOI: 10.1016/s0022-3476(73)80115-5.

23. Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. Pediatrics. 2008 Oct;122(4):831-5. DOI: 10.1542/peds.2007-2400.

24. Berg CS, Barnette AR, Myers BJ, Shimony MK, Barton AW, Inder TE. Sodium bicarbonate administration and outcome in preterm infants. J Pediatr. 2010 Oct;157(4):684-7. DOI: 10.1016/j.jpeds.2010.05.019.

25. Papile LA, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. J Pediatr. 1978 Nov;93(5):834-6.
DOI: 10.1016/s0022-3476(78)81096-8.

26. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015 Nov 3;132(18 Suppl 2):S543-60.
DOI: 10.1161/CIR.0000000000000267.

27. Liu Y, Chai Y, Rong Z, Chen Y. Prognostic Value of Ionized Calcium Levels in Neonatal Sepsis. Ann Nutr Metab. 2020;76(3):193-200.
DOI: 10.1159/000508685. Epub 2020 Aug 5.

28. Yılmaz B, Aygün C, Çetinolu E. Vitamin D levels in newborns and association with neonatal hypocalcemia. J Matern Fetal Neonatal Med. 2018 Jul;31(14):1889-1893.

DOI: 10.1080/14767058.2017.1331430. Epub 2017 Jun 14.

29. Mehrotra P, Marwaha RK, Aneja S, Seth A, Singla BM, Ashraf G, et al. Hypovitaminosis d and hypocalcemic seizures in infancy. Indian Pediatr. 2010 Jul;47(7):581-6. DOI: 10.1007/s13312-010-0131-1. Epub 2009 Oct 14.

30. Mestman JH. Parathyroid disorders of pregnancy. Semin Perinatol. 1998 Dec;22(6):485-96.
DOI: 10.1016/s0146-0005(98)80028-1.