Hypocalcemia in Newborns

Calcium (Ca) is actively transferred from mother to fetus during last trimester, as demonstrated by a significantly higher level of total Ca concentration in cord blood compared to maternal serum.[1] Parathyroid hormone (PTH) and calcitonin (CT) do not cross the placental barrier. PTH related peptide (PTHrP) is the main regulator of the positive Ca balance across the placenta. Serum Ca (SCa) in the fetus is 10 to 11 mg/dL at term (1 to 2 mg/dL higher as compared to mother).

After birth, the SCa levels in newborns depend on the PTH secretion, dietary calcium intake, renal calcium reabsorbtion, and skeletal calcium and vitamin D status. Hence, after delivery, SCa levels start decreasing (the rate and extent of decrease is inversely proportional to the gestation) and reaches a nadir of 7.5 to 8.5 mg/dL in healthy term babies by day 2 of life. This postnatal drop in SCa may be related to decreased PTH level, end organ unresponsiveness to PTH[2], abnormalities of vitamin D metabolism, hyperphosphatemia, hypomagnesemia, and hypercalcitonemia, which occur by 12-24 hours of age. [3]

PTH levels increase gradually in the first 48 hours of life and normal levels of SCa are achieved by 3rd day of life.[4] The efficacy of the intestinal absorption and the renal handling of Ca mature by 2 to 4 weeks. This transition phase is responsible for the increased risk of early onset hypocalcemia in high-risk neonates.

Calcium homeostasis in newborn

Body Ca exists in two major compartments: skeleton (99%) and extracellular fluid (1%). Ca in the extracellular fluid is present in three forms[5]:

- Bound to albumin (40%)
- Bound to anions like phosphorus, citrate, sulfate and lactate (10%) *and*
- Free ionized form (50%)

Ionized serum calcium (iSCa) is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity.

Measurement of the total serum Ca (tSCa) concentration alone can be misleading because the relationship between tSCa and iSCa is not always linear. Correlation between two is poor when the serum albumin concentration is low and, to a lesser degree, with disturbances in acid-base status, both of which occur frequently in premature or sick infants. With hypoalbuminemia, tSCa is low while iSCa is normal. Falsely low iSCa may be recorded in alkalosis and with heparin contamination of blood sample. In general, the tSCa falls by 0.8 mg/dL (0.2 mmol/L) for every 1.0 g/dL fall in the plasma albumin concentration.

Therefore, estimation of tSCa is a poor substitute for measuring the iSCa.

Definition

Hypocalcemia is defined by different tSCa and iSCa cutoffs for preterm and term infants (Table 1).[6]

Panel 1: Definition of hypocalcemia

Gestation of infants	Total serum calcium level	Ionic serum calcium level
Preterm	<7 mg/dL (1.75 mmol/L)	<4 mg/dL (1 mmol/L)
Term	<8 mg/dL (2 mmol/L; total)	<4.8 mg/dL (1.2 mmol/L)

The SCa is usually reported in different units viz. mg/dL, mEq/L and mmol/L The relationship between these units is related to the following equations:

mmol/L = [mg/dL x 10] ÷ molecular wt

mEq/L = mmol/L x valency

Since the molecular weight of Ca is 40 and the valence is +2, 1 mg/dL is equivalent to 0.25 mmol/L and to 0.5 mEq/L. Thus, values in mg/dL may be converted to molar units (mmol/L) by dividing it by 4.

Early onset neonatal hypocalcemia (ENH)

Table 1 Causes of early onset hypocalcaemia

Prematurity
Preeclampsia
Infant of diabetic mother
Perinatal stress/ asphyxia
Maternal intake of anticonvulsants (phenobarbitone, phenytoin sodium)
Maternal hyperparathyroidism
Iatrogenic (alkalosis, use of blood products, diuretics, phototherapy, lipid infusions etc)

This condition is fairly common and seen within the first 3 to 4 days of life in following clinical settings (Table 1):

Prematurity: This may be related to premature termination of trans-placental supply, exaggeration of the postnatal drop to hypocalcemic levels, increased calcitonin and diminished target organ responsiveness to parathyroid hormone.

Infant of diabetic mother (gestational and insulin dependent): This may be related to increased calcium demands of a macrosomic baby.[7] Magnesium depletion in mothers with diabetes mellitus causes hypomagnesemic state in the fetus. This hypomagnesemia induces functional hypoparathyroidism and hypocalcemia in the infant. A high incidence of birth asphyxia and prematurity in infants of diabetic mothers are also contributing factors.

Perinatal asphyxia: Delayed introduction of feeds, increased calcitonin production, increased endogenous phosphate load, renal insufficiency, and diminished parathyroid hormone secretion- all may contribute to hypocalcemia**.**

Maternal hyperparathyroidism: This causes intrauterine hypercalcemia suppressing the parathyroid activity in the fetus resulting in impaired parathyroid responsiveness to hypocalcaemia after birth. Hypocalcaemia may be severe and prolonged.

Intrauterine growth restriction (IUGR): Infants with IUGR may have hypocalcemia if they are born preterm and/or have had perinatal asphyxia**.** ***IUGR or Small for gestational age (SGA) is not an independent risk factor for ENH*****.**

Maternal anticonvulsants: Intake of anticonvulsants like phenobarbitone and phenytoin alters the vitamin D metabolism and predisposes them to its deficiency. The infants of epileptic mothers may be at risk of neonatal hypocalcemia. It can be prevented by vitamin D supplementation to mothers.

Iatrogenic: Any condition causing alkalosis increases the binding of the calcium with albumin and causes decrease in iSCa.

There is no universal recommendation regarding routine screening of at-risk infants for ENH. However following categories of infants may be considered for the same:

(a) Preterm infants born before 32 wks
(b) Infants of diabetic mothers
(c) Infants born after severe perinatal asphyxia defined as Apgar score < 4 at 1 minute of age

Time schedule for screening: at 24 and 48 hours of age risk babies.

Clinical presentation:

Asymptomatic: ENH is usually asymptomatic unlike the late onset variety and is incidentally detected.

Symptomatic: The symptoms may be of neuromuscular irritability - myoclonic jerks, jitteriness, exaggerated startle, and seizures. They may represent the cardiac involvement like- tachycardia, heart failure, prolonged QT interval, decreased contractibility. More often they are non-specific and not related to the severity of hypocalcemia. Apnea, cyanosis, tachypnoea, vomiting and laryngospasm are other symptoms that are noted.

Diagnosis

Laboratory: by measuring total or ionized serum calcium. Ionized calcium is the preferred mode for diagnosis of hypocalcemia.

ECG: QoTc >0.22 seconds or QTc >0.45 seconds

$$QTc = \frac{\text{QT interval in seconds}}{\sqrt{\text{R-R interval in seconds}}}$$

$$QoTc = \frac{\text{QoT interval in seconds}}{\sqrt{\text{R-R interval in seconds}}}$$

(QT interval is measured from origin of q wave to end of T wave on ECG; QoT is measured from origin of q wave to origin of T wave).

A diagnosis of hypocalcemia based only on ECG criteria is likely to yield a high false positive rate. Although these parameters have good correlation with hypocalcaemia in low birth weight infants (sensitivity of 77% and specificity of 94.7%)[8], neonates suspected to have hypocalcemia by ECG criteria should have the diagnosis confirmed by measurement of serum calcium levels.

Treatment of early onset hypocalcemia (Figure 1)

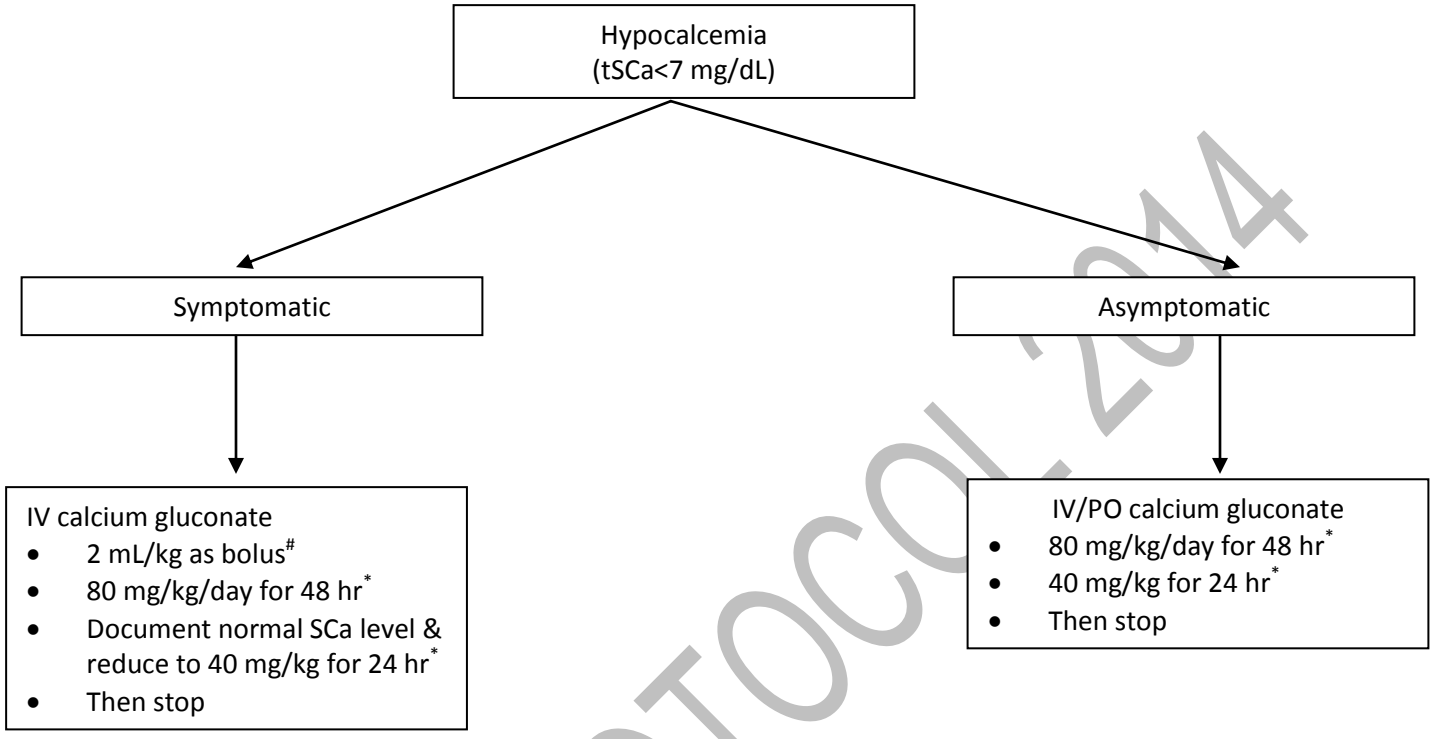
Patients at increased risk of hypocalcemia: Preterm infants (≤32 weeks), sick infants of diabetic mothers and those with severe perinatal asphyxia should receive 40 mg/kg/day of elemental calcium (4 mL/kg/day of 10% calcium gluconate) for prevention of early onset hypocalcemia. However there is not sufficient evidence for this practice. Infants tolerating oral feeds may receive this calcium orally q 6 hourly. Therapy should be continued for 3 days. Oral calcium preparations have high osmolality and should be avoided in babies at higher risk of necrotizing enterocolitis.

***Patients diagnosed to have asymptomatic hypocalcemia*:** Infants detected to have hypocalcemia on screening and who are otherwise asymptomatic should receive 80-mg/kg/day elemental calcium (8 mL/kg/day of 10% calcium gluconate) for 48 hours (Algorithm 1). This may be tapered to 50% dose for another 24 hours and then discontinued. Neonates tolerating oral feeds may be treated with oral calcium (IV preparation may be used orally).

***Patients diagnosed to have symptomatic hypocalcemia*:** These patients should receive a bolus dose of 2 mL/kg/dose diluted 1:1 with 5% dextrose over 10 minutes under cardiac monitoring. When there is severe hypocalcaemia with poor cardiac function, calcium chloride 20 mg/kg may be given through a central line over 10-30 minutes (as chloride in comparison to gluconate does not require the metabolism by the liver for the release of free calcium). This should be followed by a continuous IV infusion of 80 mg/kg/day elemental calcium for 48 hours. Continuous infusion is preferred to IV bolus doses (1 mL/kg/dose q 6 hourly). Calcium infusion should be dropped to 50% of the original dose for the next 24 hours and then discontinued. The infusion may be replaced with oral calcium therapy on the last day. Normal calcium values should be documented at 48 hours before weaning the infusion.

All categories of hypocalcemia should be treated for at least 72 hours. Continuous infusion is preferred to IV bolus doses. Symptomatic hypocalcemia should be treated with a continuous infusion for at least 48 hours.

Figure 1: Management of early neonatal hypocalcaemia



One mL of calcium gluconate contains 9 mg of elemental calcium

diluted 1:1 in 5% dextrose and administered under cardiac monitoring

* added to IV fluids and given as infusion. *Take care of extravasation as that can result into skin sloughing. In case of asymptomatic ENH, the same can be given PO.*

Precautions and side effects:

Bradycardia and arrhythmia are known side effects of bolus IV calcium administration. Hence, bolus doses of calcium should be diluted 1:1 with 5% dextrose and given slowly (over 10 to 30 minutes) under cardiac monitoring. An umbilical venous catheter (UVC) may be used for administration of calcium only after ensuring that the tip is positioned in the inferior vena cava. Hepatic necrosis may occur if the tip of the UVC lies in a branch of the portal vein. Umbilical artery catheter (UAC) should never be used for giving calcium injections. Accidental injection into the UAC may result in arterial spasms and intestinal necrosis.

Skin and subcutaneous tissue necrosis may occur due to extravasation. Hence, IV sites where calcium is being infused should be checked at least q 2 hourly to monitor for extravasation.

Prolonged or resistant hypocalcemia

This condition should be considered in the following situations:

- Symptomatic hypocalcemia unresponsive to adequate doses of calcium therapy
- Infants needing calcium supplements beyond 72 hours of age
- Hypocalcemia presenting at the end of the first week.

These infants should be investigated for causes of LNH (see below).

Late onset neonatal hypocalcemia (LNH)

This condition is rare as compared to ENH. It usually presents at the end of the first week of life. It is usually symptomatic in the form of neonatal tetany or seizures. This is usually caused by high phosphate intake (iatrogenic). The causes are listed in Table 2.

Table 2 Causes of late onset hypocalcemia

Increased phosphate load: cow milk, renal insufficiency
Hypomagnesemia
Vitamin D deficiency
Maternal vitamin D deficiency
Malabsorption
Renal insufficiency
Hepatobiliary disease
PTH resistence
Transient neonatal pseudohypoparathyroidism
Hypoparathyroidism

- *Primary: hypoplas*ia/aplasia (Di George's syndrome, CATCH 22 syndrome), a*ctivating* mutations of the calcium sensing receptor (CSR)
- *Secondary: maternal hy*perparathyroidism, *metabolic sy*ndromes (*Kenny-caffey* syndrome, *long-chain f*atty acyl CoA dehydrogenase deficiency, *Kearns-sayre* syndrome
- Iatrogenic: citrated blood products, lipid infusion, bicrbonate therepy, loop diuretics, glucocorticosteriods, phosphate therepy, aminoglycosides (mainly gentamicin),

Alkalosis
Phototherapy

Examination:
Such babies should have an examination with special emphasis on cataracts, hearing, and any evidence of basal ganglia involvement (movement disorder).

Investigations
These should be considered in LNH or if the hypocalcemia does not respond to adequate doses of calcium. The work up of such a case is very important to determine the etiology (Table 3).

Table 3 Investigations required in infants with persistent /late onset hypocalcaemia

First line	Second line	Others
Serum phosphate Serum alkaline phosphatase (SAP) Liver function tests Renal function tests X ray chest/ wrist Arterial pH	Serum magnesium Serum parathormone levels (PTH) Urine calcium creatinine ratio Maternal calcium, phosphate, and alkaline phosphatase	Serum magnesium Serum parathormone levels (PTH) Urine calcium creatinine ratio Maternal calcium, phosphate, and alkaline phosphatase

Table 4 Interpretation of Investigations

Disorder causing hypocalcaemia	Findings
Hypoparathyroidism	High : phosphateLow : SAP, PTH, 1,25(OH)D3
Pseudohypoparathyroidim	High : SAP, PTH, Phosphate Low : 1,25 D3
Chronic renal failure	High : phosphate, SAP, PTH, pH (acidotic), deranged RFT Low : 1,25 D3
Hypomagnesemia	High : PTH Low : phosphate, Mg,1,25 D3
VDDR1	High : SAP, PTH Low : Phosphate, 1,25 D3
VDDR II	High : SAP, 1, 25 D3, PTH Low : Phosphate

If hypocalcemia is present with hyperphosphatemia and a normal renal function, hypoparathyroidism should be strongly suspected. (See Table 4 for interpretation of diagnostic investigation.)

Treatment of LNH

The treatment of LNH is specific to etiology and may in certain diseases be life-long.

1. ***Hypomagnesemia****:* Symptomatic hypocalcemia unresponsive to adequate doses of IV calcium therapy is usually due to hypomagnesemia. It may present either as ENH or later as LNH. The neonate should receive 2 doses of 0.2 mL/kg of 50% $MgSO_4$ injection, 12 hours apart, deep IM followed by a maintenance dose of 0.2 mL/kg/day of 50% $MgSO_4$, PO for 3 days.

2. ***High phosphate load:*** These infants have hyperphosphatemia with near normal calcium levels. This happens in situation of non-huamn milk feeding (containing high phosphate content). Exclusive breast-feeding should be encouraged and top feeding with cow's milk should be discontinued. Phosphate binding gels should be avoided.

3. ***Hypoparathyroidism[9]:*** These infants tend to be *hyperphosphatemic and hypocalcemic with normal renal function*. Elevated phosphate levels in the absence of exogenous phosphate load (cow's milk) and presence of normal renal functions, indicates parathormone inefficiency.

   It is important to realize that if the phosphate level is very high, then adding calcium may lead to calcium deposition and tissue damage. Thus attempts should be made to reduce the phosphate (so as to keep the calcium and the phosphate product less than 55).[10] These neonates need supplementation with calcium (50 mg/kg/day in 3 divided doses) and 1,25$(OH)_2$ vitamin D_3 (0.5-1 μg/day). Syrups with 125 mg and 250 mg per 5 ml of calcium are available. 1, 25$(OH)_2$ vitamin D_3 (calcitriol) is available as 0.25 μg capsules. Therapy may be stopped in hypocalcemia secondary to maternal hyperparathyroidism after 6 weeks.

4. ***Vitamin D deficiency states:*** These babies have hypocalcemia associated with hypophosphatemia due to an intact parathormone response on the kidneys. They benefit from Vitamin D_3 supplementation in a dose of 30-60 ng/kg/day.

Monitoring

The baby is monitored for the SCa, and phosphate, 24 hour urinary calcium, and calcium creatinine ratio. Try to keep the calcium in the lower range as defective distal tubular absorption leads to hypercalciuria and nephrocalcinosis.[11]

Prognosis and outcome

Most cases of ENH resolve within 48-72 hours without any clinically significant sequelae.

LNH secondary to exogenous phosphate load and magnesium deficiency also responds well to phosphate restriction and magnesium repletion. When caused by hypoparathyroidism, hypocalcemia requires continued therapy with vitamin D metabolites and calcium salts. The period of therapy depends on the nature of the hypoparathyroidism which can be transient, last several weeks to months, or be permanent.

Research needs

Panel 2 provides researchable issues in neonatal hypocalcemia.

Panel 2 : List of researchable issues in neonatal hypocalcemia

S.NO	Research question	Type of study	Intervention	Outcome measures
1.	What is the incidence of neonatal hypocalcemia, age at onset, clinical manifestations and short term outcomes? (Epidemiology of hypocalcemia)	Cohort study by enrolling at risk infants (Table 1 and 2)	Nil	Incidence, Age at which it is detected in hours, Rate of occurrence of different clinical manifestation, Neurological examination at discharge, Risk factors
2	What is long term outcomes of neonatal hypocalcemia?	Infants with hypocalcemia and gestation matched infants without hypocalcemia	Nil	Neurodevelopment at 18 months
3	Does routine prophylactic calcium supplementation in at-risk babies reduces the incidence of neonatal hypocalcemia?	Randomized control trial	Group1: Prophylactic calcium supplementation at 40 mg/kg/dL to at-risk babies Group 2: No calcium	• Incidence of asymptomatic and symptomatic hypocalcemia. • Complications of therapy such as thrombophlebitis, arrhythmias, gastro intestinal side effects and nephrocalcinosis

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