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Case Report

A Case of Severe Neonatal Hypocalcemia Treated With Continuous Enteral Calcium

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ABSTRACT

Background/Objective: Hypocalcemia is a common, treatable cause of neonatal seizures. The rapid repletion of calcium is essential for restoring normal calcium homeostasis and resolving seizure activity. The accepted approach to administer calcium to a hypocalcemic newborn is via peripheral or central intravenous (IV) access.

Case Report: We discuss a case of a 2-week-old infant who presented with hypocalcemia and status epilepticus. The etiology was determined to be neonatal hypoparathyroidism secondary to maternal hyperparathyroidism. Following an initial dose of IV calcium gluconate, the seizure activity abated. However, stable peripheral intravenous access could not be maintained. After weighing the risks and benefits of placing a central venous line for calcium replacement, it was decided to use continuous nasogastric calcium carbonate at a rate of 125 mg of elemental calcium/kg/d. Ionized calcium levels were used to guide the course of the therapy. The infant remained seizure-free and was discharged on day 5 on a treatment regimen that included elemental calcium carbonate, calcitriol, and cholecalciferol. He remained seizure free since discharge and all medications were discontinued by 8 weeks of age.

Discussion: Continuous enteral calcium is an effective alternate therapy for restoration of calcium homeostasis in a neonate presenting with hypocalcemic seizures in the intensive care unit (ICU).

Conclusion: We propose that continuous enteral calcium be considered as an alternative approach for calcium repletion in neonatal hypocalcemic seizures, one that avoids the potential complications of peripheral or central IV calcium administration.

Introduction

Neonatal hypocalcemia, defined as a total serum calcium <8 mg/dL (2 mmol/L) or ionized calcium <4.4 mg/dL (1.1 mmol/L) for term infants,[1] is a common metabolic problem in the newborn period.[1,2] It can be caused by congenital hypoparathyroidism (transient or permanent), pseudohypoparathyroidism (transient or permanent), hypo- or hypermagnesemia,[3-6] dietary phosphate overload, and vitamin D deficiency.[7] Most formula-fed infants with hypocalcemia have underlying endocrinologic disturbances as opposed to nutritional deficiencies, a circumstance accounted for by the advent of increased attention to the phosphorus, calcium, and magnesium content in infant formulas.[7] Exclusively breast-fed infants are at higher nutritional risk when not using vitamin D supplementation.[8]

The standard repletion of calcium in hypocalcemic seizures is intravenous (IV) calcium gluconate, administered as an initial IV bolus followed by a continuous IV calcium infusion.[1,3] Clinical outcomes for infants presenting with hypocalcemic seizures are good, with resolution of symptoms reported within days to weeks following calcium administration.[7] Neonates with hypoparathyroidism are identified by an inappropriately low or normal parathyroid hormone (PTH) level in the face of hypocalcemia.

The use of continuous enteral calcium to treat acute symptomatic hypocalcemia in neonates is not recommended by standard

Abbreviations: $CaCO_3$, calcium carbonate; CaSR, calcium-sensing receptor; CT, computerized tomography; EEG, electroencephalogram; IM, Intramuscular; IV, Intravenous; NG, nasogastric; PICC, Percutaneously inserted central catheter; PICU, pediatric intensive care unit; PTH, parathyroid hormone.

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sources.[4,9] In fact, our review of the literature identified no cases in which the use of enteral calcium to treat neonatal hypocalcemia was reported. This is most likely based on the rapidity with which IV calcium raises serum calcium, a function of its 100% bioavailability as opposed to variable enteral absorption. However, if IV replacement is the only option for treatment, and the healthcare team is unable to promptly secure peripheral IV access, or if peripheral IV access is lost and cannot be replaced, then central IV access would be required. The latter carries multiple inherent risks in the neonate (ie, bloodstream infection, thromboembolism, malposition, catheter occlusion).[10-12] Establishing that continuous enteral calcium combined with enteral calcium boluses can successfully treat acute symptomatic hypocalcemia in neonates offers the ability to avoid delay in initiating treatment while decreasing the risk of complications associated with central IV access in young patients.

Highlights

- Neonatal hypocalcemia is a common cause of neonatal seizures that requires prompt calcium repletion.
- Symptomatic hypocalcemia is traditionally treated with one or more intravenous calcium boluses followed by a maintenance intravenous calcium infusion until calcium levels are stabilized.
- Nasogastric calcium repletion is an effective treatment alternative in cases of neonatal hypocalcemia.
- Calcium repletion via nasogastric route avoids complications of peripheral or central intravenous calcium administration like infections, phlebitis, occlusion, or infiltration.

Clinical Relevance

Neonatal hypoparathyroidism can cause hypocalcemia that is classically treated with intravenous calcium. This case illustrates the management of a neonate with hypoparathyroidism successfully treated with enteral calcium repletion after initial stabilization. We propose continuous enteral calcium as an alternate, safe, and effective mechanism of calcium repletion avoiding complications of intravenous calcium.

Case Report

A 2-week old male infant was admitted to an outside hospital in status epilepticus with tonic-clonic seizures. He had begun having rhythmic movements at home on the third day of life, with progressive worsening and lengthening of episodes. These episodes, as well as development of circumoral cyanosis, prompted the family to seek medical attention.

The infant was born full-term via induced vaginal delivery with a birthweight of 3 kg. Results of the newborn screen were normal. Maternal history was notable for hypercalcemia in the 12 mg/dL range with parathyroid gland. She also had hypercalcemia in her previous 2 pregnancies and was awaiting surgery for parathyroidectomy at the time of delivery.

Following arrival at the outside hospital, the infant was given lorazepam, dextrose-containing IV fluids, a phenobarbital loading dose, and 1 dose of ampicillin and gentamicin. He was noted to have hypocalcemia, with a serum calcium of 5.6 mg/dL (1.4 mmol/L) (7.8-11.3 mg/dL, 1.9-2.8 mmol/L), and an otherwise normal chemistry. He received an IV calcium bolus and was then transferred to a pediatric hospital. In the emergency department, the infant was afebrile, normotensive, tachycardic (153 beats per minute), and tachypneic (40 breaths per minute). Physical examination findings were otherwise normal.

During the transfer to our hospital, peripheral IV access was lost. On laboratory work-up upon arrival, he was found to have persistent hypocalcemia, with a serum calcium of 5.8 mg/dL (1.45 mmol/L) (7.8-11.3 mg/dL, 1.9-2.8 mmol/L) and an ionized calcium of 0.89 mmol/L (1.12-1.32 mmol/L). Serum magnesium was low at 1.1 mEQ/L (1.1 mmol/L) (1.3-1.9 mEQ/L, 0.57-1.12 mmol/L) and serum phosphorus was normal at 7.2 mg/dL (2.3 mmol/L) (3.4-5.9 mg/dL, 1.4-3 mmol/L). Urinary calcium was 1.9 mg/dL (0.47 mmol/L) and urinary creatinine was 8 mg/dL (0.71 mmol/L) with a calcium to creatinine ratio of 0.24 mg/mg (0.66 mol/mol) (0.03-0.81 mg/mg, 0.09-2.2 mol/mol).[13] Following initial stabilization and treatment, a serum PTH level obtained on admission was found to be inappropriately low-normal given the patient's hypocalcemia at 19 pg/mL (reference range 15-65 pg/mL). In the face of the maternal history, the patient's diagnosis was identified as hypoparathyroidism secondary to maternal hyperparathyroidism.

The patient was admitted to the pediatric intensive care unit (PICU). Given significant difficulty obtaining new peripheral IV access after the initial access was lost, a conversation ensued between the pediatric endocrinology and intensive care teams. After weighing the risks and benefits of placing a central venous line for calcium replacement in such a young patient, it was decided instead to treat via an enteral route. The patient was no longer seizing but was at high risk of seizure recurrence. The PICU physician was available if needed to insert an urgent central line at any sign of inadequate enteral calcium replacement. Treatment was initiated with continuous NG calcium carbonate ($CaCO_3$) (a suspension of 100 mg/mL) using an enteral syringe pump at a dose of 125 mg of elemental calcium/kg/d. He was given NG $CaCO_3$ boluses (5 in total) in an effort to maintain normal ionized calcium levels, which were closely monitored via iSTAT (Fig.). The rate of improvement of ionized calcium was 0.15 mmol/L/24 h and the rate of improvement in total calcium was 1.33 mg/dL/24 h. Given the diagnosis of hypoparathyroidism and hypomagnesemia, treatment included enteral calcitriol and magnesium replacement.

The infant remained stable and was discharged 5 days after admission on elemental calcium carbonate (54 mg/kg/d), calcitriol (25 ng/kg/d), and cholecalciferol (2000 International Units daily). He has been seizure free and normocalcemic, and all medications were discontinued by 8 weeks of age.

Discussion

The management of neonatal seizures due to hypocalcemia begins by establishing the cause of hypocalcemia and immediately replacing calcium to increase serum levels.[1] Typically, elemental calcium of 10 to 20 mg/kg (1-2 mL/kg/dose of 10% calcium gluconate) is given via slow IV infusion to patients with symptomatic hypocalcemia.[1] The initial calcium infusion aims to prevent further seizures but will not persistently normalize serum calcium levels.[1] Thus, after the initial calcium boluses, a continuous infusion of 50 to 100 mg of elemental calcium/kg/d is recommended.[14] It is recommended to transition to oral calcium only when serum calcium levels are stabilized. For parenteral calcium replacement, calcium gluconate is preferred due to the severity of soft tissue and skin necrosis that can occur with extravasation of calcium chloride.[15] However, extravasation of calcium gluconate can also cause rapid and marked swelling and erythema, with local soft tissue necrosis and secondary infection, and subsequent extensive local calcification, known as calcinosis cutis.[16] In addition, rapid administration of IV calcium can induce serious arrhythmias such as bradycardia or

Timeline of serum calcium levels and treatment with enteral calcium.

Time	Baseline	1.5h	5.5h	10h	13.5h	15h	20h	25h	35.5h	41h	53h	65h	77h
$CaCO_3$ infusion				125 mg elemental Ca/kg/day									
$CaCO_3$ bolus (mg elemental Ca/kg)		58 mg/kg	100 mg/kg	100 mg/kg	100 mg/kg	100 mg/kg		100 mg/kg q6hr		75 mg/kg q6hr			70 mg/kg q6hr
Ionized calcium (mmol/L)	0.89	0.83	0.9	0.94	0.94	0.92	0.92	0.97	1.02	1.15	1.25	1.31	
Total calcium (mg/dL)	5.8											9.4	9.6

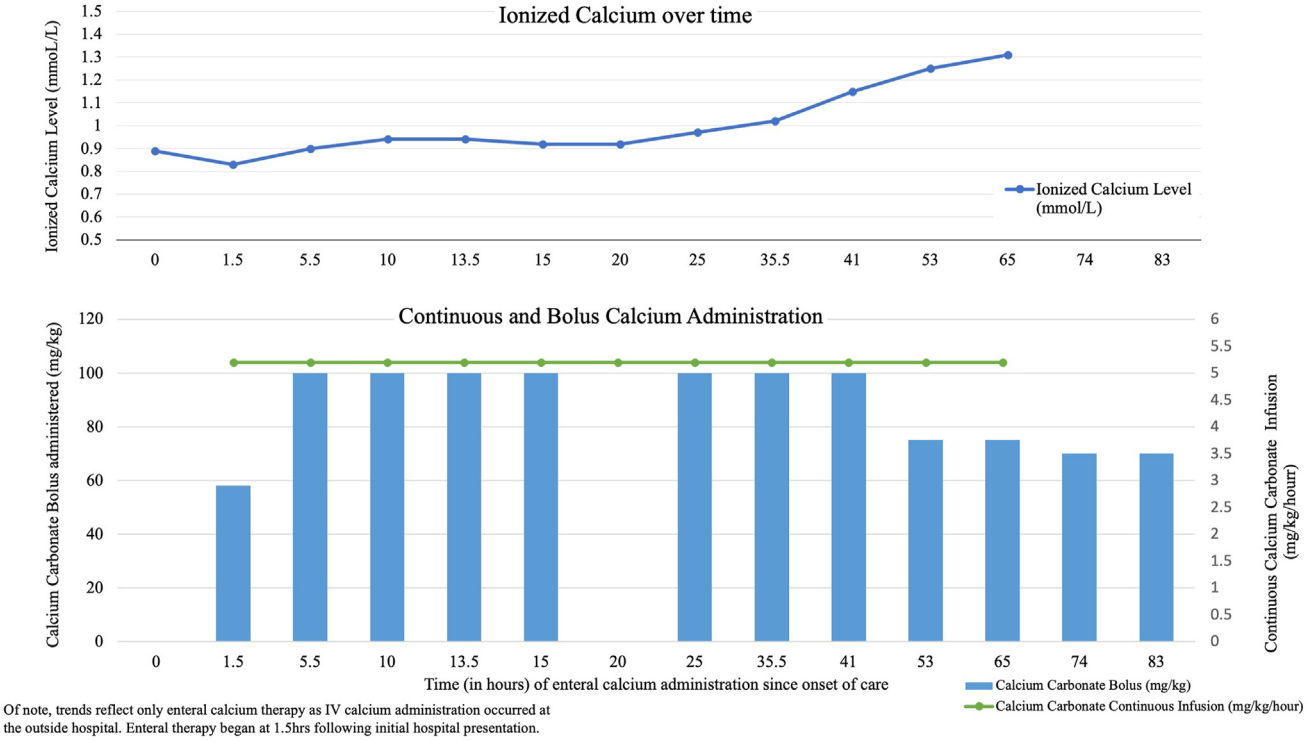

Fig. 1. Graph of ionized calcium level and enteral calcium carbonate dose administered (continuous and bolus) from the time since arrival at pediatrics hospital.

ventricular tachycardias such as torsade de pointes. Thus, patients should be closely monitored for arrythmias.[17]

Apart from potential severe skin injury due to extravasation of calcium solutions via peripheral IV catheters, both peripheral and central IV lines are associated with other documented complications. Complications associated with peripheral IV lines include line-associated bloodstream infections, phlebitis, occlusion, or soft tissue infiltration.[10] The incidence of venous thromboembolism due to central venous catheters is as high as 9.2% in ill neonates in the PICU[18] and there is a risk of central venous catheter related bloodstream infections. Percutaneously inserted central catheters (PICCs) are also commonly used in neonates and infants who need central venous access. However, the complications associated with PICCs in infants include infection, clot formation, malposition, and malfunction and/or occlusion.[12,19] More serious and rare side effects including arrhythmias, movement of the catheter tip into other organ tissues such as the pleura, pericardium, or peritoneum, as well as embolization of portions of the line have also been reported.[12] Complications of PICC lines may occur in as many as a third of infants.[12]

In the present case, difficulty in maintaining peripheral IV access and concern about extravasation of calcium, led to consideration of central access and a discussion of the associated risks. This discussion occurred in the setting of persistent hypocalcemia and risk for seizure recurrence, but no active seizures. It was decided to treat with continuous enteral calcium in addition to enteral calcium boluses via NG tube. We recognized that this was an unconventional approach. In general, oral calcium therapy is reserved for patients who are asymptomatic or have been acutely treated with IV calcium and require maintenance therapy. Indeed, there was an initial concern that enteral calcium may not raise serum calcium and thus resolve clinical symptoms as rapidly as IV calcium treatment. To compensate for the known decreased enteral absorption, in addition to treating with calcitriol, we purposefully treated our

patient with a daily calcium dose higher than the one typically used with IV calcium, which has 100% bioavailability. Despite the calcium levels showing a relatively slow initial rate of rise (Fig. 1), our patient's seizures did not recur while on treatment.

Based on this case, we propose that continuous enteral calcium administration via NG tube be considered when peripheral IV access is difficult to establish or maintain, or when the treatment team wishes to avoid the small but serious potential complications of parenteral calcium infusions. We report successful treatment of hypocalcemia with continuous enteral calcium following initial parenteral treatment for our newborn patient's symptomatic hypocalcemia. We further suggest that this alternative treatment approach be explored in prospective clinical studies.

Disclosures

The authors have indicated they have no conflicts of interest relevant to this article to disclose.

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Consent was obtained from the infant's (patient) parent.

Author Contributions

Dr Donner and Dr Ganta conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Polikoff, Snelling and Serrano-Gonzalez conceptualized and designed the study, interpreted data, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability

All data used in this manuscript are available within the article.

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