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REVIEW ARTICLE

Hypocalcemia in the Critically Ill Pediatric Patients: A Review

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Abstract

Hypocalcemia is common in the critically ill pediatric patients. However, the diagnosis of hypocalcemia in this population is complicated by interpretation of the total plasma calcium concentration. These limitations are principally the result of the effects of hypoalbuminemia and disorders of acid-base balance on the total calcium concentration. Thus, measurement of ionized calcium can be critical in determining an individual's true serum calcium status. In this review, we first described the regulation of normal calcium metabolism and then focus on the various etiologies of hypocalcemia, which are encountered in the pediatric critical care settings. The approach to the treatment of hypocalcemia and the current consensus on treatment of hypocalcemia in the critically ill pediatric patient is also presented.

Key words: *Critical illness, hypocalcemia.*

Introduction

Calcium has widespread extra and intracellular actions, including effects that influence hormone secretion and responsiveness, enzyme activity, nerve conduction, muscle contraction, and membrane potential. In addition, calcium plays a structural role as a component of the mineralized matrix of bone. Although a highly regulated system exists to maintain extracellular concentrations of ionized calcium within narrow physiological range, hypocalcemia is common in pediatric critically ill patients.[1-3] However, obvious metabolic defects in the hormonal control of calcium homeostasis (such as hypoparathyroidism or vitamin D deficiency) or physicochemical disturbances (such as massive transfusions precipitating calcium chelation) are present in a small subset of critically ill pediatric patients. More frequently, the precise basis for hypocalcemia is unknown. For instance, hypocalcemia is common in sepsis,[4-6] and when circulating cytokines that accumulate during sepsis can impair parathyroid hormone secretion.[7,8] In this article, we provide the guiding principles of calcium hemostasis and describe our current understanding of the pathophysiology of hypocalcemia in the critically ill paediatric patients.

The majority (99%) of total body calcium is stored in bone as (1) hydrtoxyapatite crystals and (2) to a lesser extent, as non-crystalline, readily mobilizable calcium salts. The remainder resides within extracellular fluids and soft tissues. At normal serum protein concentrations, approximately 50% of total serum calcium is in ionized form, biologically active (Ca2+). An additional 8% to 10% is complexed to organic and inorganic acids (e.g., citrate, sulphate, and phosphate). The remaining 40% of serum calcium is protein-bound, primarily to albumin (80%) and also to globulins (20%) and is not biologically active.[9] Changes in the ionized component of serum

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calcium are responsible for symptoms related to hypocalcemia. Increases in extracellular fluid concentrations of anions such as phosphate, citrate,

bicarbonate, or edetic acid, will chlelate calcium and decreases the concentrations of ionic calcium but will not affect the total calcium concentration. Similarly an alkaline pH will reduce the Ca2+ via an increase in the affinity of albumin for calcium, without altering the total serum calcium. Acidosis has the opposite effect. Free fatty acids also enhance the binding of calcium to albumin.[10]

Overall calcium homeostasis is controlled by a complex feedback system. Parathyroid hormone directly targets the bone resorption and renal calcium reabsorption and indirectly by stimulating renal[1-3] hydroxylase, the rate-limiting enzyme in vitamin D activation, to convert 25-hydroxyvitamin D into calcitrol. Renal tubules typically resorb about 99% of filtered calcium in the cortical portion of the thick ascending limb. Parathyroid hormone and calcitrol regulate active transport by increasing activity and/or expression of multiple calcium transport proteins in the distal nephron.[11]

Hypocalcemia

Neuromuscular irritability is the hallmark of hypocalcemia and manifests as tetany, a condition characterized by circumoral numbness, distal extremity paresthesias, and muscle cramps. When hypocalcemia is severe, patients may experience bronchospasm or laryngospasm that mimics asthma. Localized or generalized seizures as well as more vague symptoms as hyperirritability may also occur. Hypocalcemia delays ventricular depolarization and prolongs the Q-T and ST intervals on the ECG and rarely, a reversible form of congestive cardiac failure may develop.

Early neonatal hypocalcemia, which occurs within first 3 days of birth, arises from inadequate secretion of parathormone (PTH) by immature parathyroid glands,[12] and/or inadequate responsiveness of the renal tubule cells to PTH. Risk factors include prematurity,[13] low birth weight,[14] and maternal diabetes mellitus.[15] A more severe form of transient neonatal hypoparathyroidism occurs in infants born to mothers with hypercalcemia.[16] Neonatal hypocalcemia that occurs after the first 3 to 5 days of life classically arises from an excessive phosphate intake in infants who are fed cow's milk or cow's milk-based infant formulas.[17] The ensuing hyperphosphatemia leads to hypocalcemia. Transient hypoparathyroidism may also manifest during this time. Less commonly maternal hypercalcemia, congenital defects in PTH production, secretion, or action, and specific magnesium deficiency disorders can cause neonatal hypocalcemia.[16]

Congenital defects in parathyroid gland development may be isolated or, more commonly, occur in association with other developmental defects. In particular, syndromic hypoparathyroidism must be considered in infants and children with congenital heart defects, deafness, or immune defects. The extent of the parathyroid gland abnormality largely dictates whether hypoparathyroidism develops. For some individuals, hypoparathyroidism may only be unmasked with increased demands for PTH during growth or during intercurrent illness. The most common cause of congenital hypothyroidism is the DiGeorge syndrome, also known as velocardiofacial syndrome. The complete DiGeorge syndrome refers to the triad of congenital absence of the thymus, congenital hypoparathyroidism, and cardiac anomalies, commonly of the outflow tract or aortic arch,[18] heterozygous deletion of 22q11.2 is the most common cause with an incidence of 1 in 2000 to 4000 births. Familial occurrence of DiGeorge syndrome has been described. Other chromosomal abnormalities and teratogens have also been implicated in the DiGeorge syndrome. The degree of parathyroid hypoplasia is variable, many infants experience spontaneous improvement in parathyroid function and have normal serum calcium levels, while some patients do not develop parathyroid dysfunction until much later in life.[19] When spontaneous resolution of hypoparathyroidism occurs in infancy, hypocalcemia may occur years later during conditions of stress.[20]

Hypocalcemia in critical illness

Hypocalcemia is common in critically ill pediatric patients. In some cases, the basis will be clear: acute renal insufficiency, fluid overload after dialysis, transfusion with citrated blood or alkalosis. There are many drugs associated with hypocalcemia. Chemotherapeutic agents such as the use of 5-fluorouracil may result in mild hypocalcemia.

Cisplatinum, as well as many diuretics, can induce hypomagnesemia and thereby cause hypocalcemia.

For the majority of patients, hypocalcemia reflects a hypoalbuminemic state.[21] The cause or pathophysiology of hypocalcemia will not be readily apparent; in a study, >50% of patients had no identifiable etiology for the hypocalcemia.[22] Sepsis is a well-recognized risk factor for hypocalcemia. In nonseptic, critically ill patients hypocalcemia (defined as ionized calcium <1.16 mmol/L) has also been recognized.[4] Vitamin D deficiency as well as acquired, "relative" hypoparathyroidism, vitamin D resistance, and 1- hydroxylase deficiency are proposed mechanisms for hypocalcemia in critically ill pediatric patients.[7,22]

Patients with toxic shock syndrome or gram-negative bacterial sepsis may have elevated levels of tumor necrosis factor (TNF-α) that have also been associated with hypocalcemia. These observations suggest that increased sensitivity of parathyroid cells to the extracellular Ca2+ concentration can provide a mechanism for hypocalcemia in the setting of an inflammatory process such as sepsis. The direct contribution, if any, of hypocalcaemia to decreased survival is still being explored. In the pediatric populations, ionized hypocalcemia has been associated with more severe illness.[1] Thus hypocalcemia may be a marker of greater disease severity rather than a cause of increased mortality. Although neuronal irritability, a classic sign of hypocalcaemia is absent in critically ill patients with hypocalcaemia,[7] the relevance of this finding to other pathological effects of hypocalcaemia is not known. Perhaps most relevant to critically ill patients, hypocalcaemia has been shown to contribute to cardiac dysfunction and hypotension,[7,23] and case reports of cardiomyopathy and heart failure reversible with chronic hypocalcemia due to hypoparathyroid states.[23,24] Additionally, calcium administration improves ventricular function in critically ill patients with ionized calcium <1.05mm0l/L.[25] Heart failure has also been associated with hypocalcemia in the setting of vitamin D-deficient rickets.[26] However, the specific contributions to cardiac function of hypophosphatemia and vitamin D, both of which are important in muscle function,[27] have not been elucidated. Because of the association of hypocalcaemia with worse clinical outcomes, and the effects of hypocalcemia on cardiovascular status, a logical question is "does treatment of hypocalcemia in critically ill patients improve outcome?" In 1995, Jankowski and Vincent reviewed the available evidence for the use of calcium in providing cardiovascular support in critically ill patients and concluded "calcium may improve cardiovascular status in critically ill patients, but at the cellular level its administration may be deleterious," and called for additional studies.[25] Nearly 15 years later, we still lack evidence-based guidance as no randomized-controlled trial has been published that examined the effect of parenteral calcium administration on mortality, other markers of poor prognosis, or complications of calcium therapy.[28] By contrast in 2000, the American Heart Association updated practice guidelines in children that restricted the administration of parenteral calcium during cardiopulmonary resuscitation to pediatric patients with hypocalcemia, hypermagnesemia, hyperkalemia, and calcium channel blocker overdose.[29]

Despite these guidelines, a recent multicenter study found that nearly 5 years after publication of the revised American Heart Association (AHA) guidelines, calcium continued to be administered to nearly half of the children during cardiopulmonary resuscitation and was associated with increased mortality and worse neurologic outcomes except in patients with metabolic abnormalities.[30] Subsequent pediatric advanced life-support guidelines published by the AHA in continue to restrict the use of calcium to specific circumstances, including hyperkalemia, documented hypocalcemia, hypermagnesemia and calcium channel blocker overdose.[31] Finally, the guidelines developed by the Surviving Sepsis Campaign do not recommend calcium administration as a therapeutic measure.[32] The common practice of administering calcium during cardiopulmonary resuscitation to individuals who do not have specific metabolic abnormalities derive from a lack of evidence of benefit plus concerns that calcium administration may lead to worse clinical outcomes. One possible explanation may be that the administration of calcium may potentiate the accumulation of cytosolic calcium, which several studies have implicated as the final common pathway of cell death.[33] For instance, brain ischemia is associated with an increase in intracellular calcium. Accumulation of intracellular calcium

through specific routes can then over activate pathways for which calcium is a second messenger, generating reactive oxygen species and trigger cell death mechanisms, reviewed by Szydlowska and Tymianski.[34] Similarly, the cardiomyocyte, reviewed by Murgia et at[35] and other cell types are subjected to this same unrestrained activation of programmed cell death and necrosis.

Treatment

In classic endocrine disorders, the approach to management of severe, symptomatic hypocalcemia is fairly straightforward. The two most commonly used calcium solutions for intravenous use are 10% calcium chloride and 10% calcium gluconate. A 10mL ampoule of 10% calcium chloride contains three times more elemental calcium (272 mg) than a 10mL ampoule of 10% calcium gluconate (90 mg). Intravenous calcium solutions are hyperosmolar and should be administered through a large central vein if possible. Calcium gluconate has a lower osmolalitly and is the preferred calcium salt to administer if a peripheral vein is used. A bolus dose of intravenous calcium gluconate (1-2 mg of elemental calcium/kg) that is administered over 5 to 10 minutes can raise the serum calcium by 0.5 to 1mg/ml. A bolus dose of calcium will raise the serum level transiently and levels will begin to fall again after 30 minutes. Therefore, a bolus dose of calcium (1-3 mg elemental calcium/kg per hour in children) then 0.5 to 1.5 mg of elemental calcium/kg per hour is administered as a continuous infusion. Individual responses to intravenous calcium will vary, so calcium dosing must be guided by periodic monitoring of the level of ionized calcium in blood. Intravenous calcium is continued until a stable oral regimen is achieved.[36]

Magnesium depletion is common in patients in intensive care units and is a frequent cause of hypocalcemia. Thus, hypomagnesemia should also be treated. The concordant administration should also be treated as activated forms of vitamin D such as calcitriol (15-50 ng/kg per day in 2-3 divided doses), can provide more stable control of the serum calcium concentration and may allow early discontinuation of intravenous calcium.[37,38]

Administration of intravenous calcium should be reserved for specific situations as this treatment can have significant risks. Patients taking digitalis may have increased sensitivity to intravenous calcium. Rapid administration of calcium can result in cardiac arrhythmias so that intravenous calcium administration should be carefully monitored. Local vein irritation can occur with solutions Ã200 mg/dl of elemental calcium. Extravasation into soft tissues can lead to inflammation and local calcification. Calcium phosphate deposition can occur in any organ and is more likely to occur if the calcium-phosphate ratio exceeds solubility product. Calcium infusions can promote vasoconstriction and ischemia of vital organs, particularly in patients with low cardiac output and preexisting poor perfusion. Excessive cytosolic calcium can induce cell death. It seems most prudent to limit the use of intravenous calcium to patients who have signs or symptoms of hypocalcemia. Chronic treatment depends on underlying etiology: calcitriol and calcium supplementation in hypoparathyroidism, and vitamin D-resistant rickets.[23] Vitamin D deficiency is treated with ergocalciferol or cholecalciferol; dosing is based partly on underlying etiology with malabsorptive disorders requiring much larger doses long term. Over replacement of calcium and/or vitamin D can cause hypercalcemia or hypercalciuria, and nephrocalcinosis and nephrolithiasis are attendant risks.

The management of hypocalcemia in the critically ill patient is more problematic: hypocalcemia may produce symptoms ranging from seizures, laryngospasm, prolonged QT, and cardiac dysfunction and intravenous calcium as described above is appropriate. Treatment of hypocalcemia in the setting of hypotension or circulatory collapse in the absence of specific hypocalcemia-attributable symptoms has been called into question, however, for concerns that such treatment may aggravate the disease process. A recent systematic review of the literature identified no studies that examined meaningful outcomes beyond increases in calcium levels following intravenous calcium administration. The concluded that “there is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients”.[29,30]

Conclusion

Hypocalcemia is common in critically ill patients. Endocrine disorders and medication side effects are common culprits, and management is generally unambiguous in such cases. Frequently, however,

the etiology of hypocalcemia in the critically ill patient is uncertain and potentially multifactorial. While mechanisms that disrupt normal calcium homeostasis are being uncovered, the precise treatment approach that ultimately benefits the critically ill patient with hypocalcemia has yet to be delineated. So, on the evidence of the role of calcium supplementation in critically ill patients highlights the need for further investigation.

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