Journal of Critical Care (2013) **28**, 810–815

ELSEVIER

Journal of Critical Care

Ionized hypocalcemia is an early event and is associated with organ dysfunction in children admitted to the intensive care unit

Cacilda Rosa Barbosa Dias MD, MSc[a], Heitor Pons Leite MD, PhD[b,*], Paulo Cesar Koch Nogueira MD, PhD[c], Werther Brunow de Carvalho MD, PhD[d]

[a]*Pediatric Intensive Care Unit, Department of Pediatrics, the Federal University of São Paulo*
[b]*Pediatric Intensive Care Unit and Discipline of Nutrition and Metabolism, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil*
[c]*Pediatric Nephrology Section, Department of Pediatrics, Federal University of São Paulo*
[d]*Instituto da Criança, University of São Paulo*

Keywords:
Hypocalcemia;
Intensive care unit;
Pediatric;
Critical illness;
Multiple organ failure;
Furosemide;
Steroids

Abstract

Purpose: The purpose was to determine the frequency and risk factors of ionized hypocalcemia and to evaluate this disturbance as a predictor of mortality in a pediatric intensive care unit (ICU).

Materials and Methods: In a prospective cohort study, 337 children admitted consecutively to an ICU were monitored regarding serum ionized calcium concentrations during the first 10 days of admission. The following variables were analyzed as independent of hypocalcemia: age; malnutrition; sepsis; Pediatric Index of Mortality 2; first 3 days organ dysfunction score (Pediatric Logistic Organ Dysfunction); and use of steroids, furosemide, and anticonvulsants. *Hypocalcemia* was defined as a serum ionized calcium concentration less than 1.15 mmol/L.

Results: The rate of hypocalcemia was 77.15%. In a multivariate model, higher Pediatric Logistic Organ Dysfunction scores during the first 3 days of ICU stay were independently associated with hypocalcemia (odds ratio, 2.24; 95% confidence interval, 1.23-4.07; $P = .008$). Medications associated with hypocalcemia were furosemide (dose ≥ 2 mg/[kg d]) and methylprednisolone (dose ≥ 2 mg/[kg d]). No significant association was found between hypocalcemia and 10-day mortality.

Conclusions: Ionized hypocalcemia is common during the ICU stay, particularly in the first 3 days of admission. This disturbance was not found to be a predictor of mortality, but it is independently associated with more severe organ dysfunction.

Hypocalcemia is one of the most clinically important electrolytic disturbances among patients admitted to the pediatric intensive care unit (ICU). It is associated with complications such as neuromuscular impairment with cramps, fasciculations and carpopedal spasms, as well as

* Corresponding author. Rua Loefgreen, 1647 zip code 04040-032, São Paulo, SP, Brazil. Tel.: +(5511) 99192 7326.
E-mail address: heitorpons@gmail.com (H.P. Leite).

0883-9441/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.03.019

paresthesias and convulsions. When hypocalcemia is severe, complications include tetany with respiratory compromise, leading to laryngospasm, stridor, and apnea. [1]. Calcium is a regulator of cellular function and essential in the process of muscle excitation-contraction, neurotransmission, and membrane stabilization [1–3]. It circulates in the bloodstream in 3 fractions: protein-bound calcium, primarily to albumin (40%); calcium bound to bicarbonate, sulfate, citrate, phosphate, and lactate ions (10%); and ionized calcium (50%), which is physiologically active [2,4,5].

The frequency of hypocalcemia in hospitalized adults ranges from 12% to 88% [5–8]. In critically ill pediatric patients in the ICU, hypocalcemia occurs in 18% to 74% [9–11]. However, the frequency reported in these studies varied according to disease type and diagnostic criteria used (total or ionized hypocalcemia) [12,13]. In critically ill pediatric patients hypocalcemia was shown to be more frequent among nonsurvivors compared to survivors [13]. This suggests that hypocalcemia may be a predictor of mortality in patients, although this association has yet to be confirmed [12,13].

Based on the premise that hypocalcemia is a common disturbance in ICU patients and given that earlier studies have involved only small and specific patient groups, yielding scant information on risk factors for ionized hypocalcemia, the aim of the present study was to ascertain the frequency and risk factors of ionized hypocalcemia in ICU pediatric patients and to determine its potential association with higher 10-day mortality.

1. Methods

A prospective cohort study of children admitted consecutively to the pediatric ICU of a teaching hospital was carried out in which serum calcium concentrations were monitored during the first 10 days of the hospital stay. All patients with a previous diagnosis of chronic renal failure, hypoparathyroidism, or brain death and those lacking data on ionized calcium levels were excluded from the study. The study site was a high-complexity unit, classed as Level 1 A according to the guidelines of the Society of Critical Care Medicine [14]. The study protocol had a prior approval from the Research Ethics Committee of the University.

Laboratory analyses of ionized calcium were performed on the first day of admission to the ICU and serially thereafter according to clinical evolution of the patients throughout their hospital stay. As part of routine care, initially, children received intravenous maintenance fluids, glucose, and electrolytes. In this solution, calcium gluconate is administered as a 10% solution at a dose of 1.0 mEq/kg. According to the ICU protocol, symptomatic hypocalcemia is treated with 10% solution of calcium gluconate 1.0 mEq/kg intravenously during 10 to 20 minutes.

The potential exposure variables for hypocalcemia were sex; age; malnutrition; Pediatric Index of Mortality 2 (PIM 2); organ dysfunction score (Pediatric Logistic Organ Dysfunction [PELOD]); sepsis and/or septic shock on admission; and use of medications that may interfere in calcium metabolism such as steroids, furosemide, and anticonvulsants. In addition, hypocalcemia was considered an exposure variable for 10-day mortality outcome.

Nutritional status was assessed using weight for age z score in children up to 2 years of age and body mass index z scores in children older than 2 years. Growth standard curves by the World Health Organization (2006-2007) [15] were used as a reference, where patients with z scores less than -2 were considered malnourished.

Clinical severity on admission was assessed based on PIM 2 prognostic score [16]. Multiple organ dysfunction from admission up to day 3 of the ICU stay was clinically assessed using the PELOD score [17].

Sepsis and septic shock diagnoses were defined based on the criteria of the International Pediatric Sepsis Consensus Conference [18].

Drugs that could interfere with calcium metabolism were recorded for the first 3 days of the ICU stay, namely, furosemide (dose ≥ 2 mg/[kg d]), methylprednisolone (dose ≥ 2 mg/[kg d]), and the anticonvulsants phenytoin and/or phenobarbital (at any dose).

Ionized calcium analysis was performed using the ion selection method on an EML 100 electrolyte analyzer (Radiometer, Copenhagen, Denmark) [19]. *Hypocalcemia* was defined as a serum ionized calcium concentration less than 1.15 mmol/L.

Because calcium is involved in numerous metabolic reactions, various situations can mimic manifestations of hypocalcemia including convulsions, cardiac arrhythmia, and tetany. These clinical manifestations and their complications were not addressed in the present study because they cannot be exclusively attributed to hypocalcemia, presenting in other situations commonly encountered in the ICU.

1.1. Statistical analysis

Sample size was based on a study in the literature describing a 2.7-fold greater risk of mortality in adult hypocalcemic patients on admission to an ICU [12]. Based on this magnitude of risk, a 95% confidence interval (CI), and 80% study power, the required sample size was estimated at 287 patients. Continuous quantitative variables were expressed as median and interquartile range, whereas categorical variables were expressed as frequencies. For the analysis of exposure variables for hypocalcemia, PIM 2 and PELOD scores were converted into categorical variables in which the median value of the distribution was taken as cutoff points. The association between each independent categorical variable and the hypocalcemia outcome (yes/no) was determined by univariate analysis of each risk factor against the outcome using the χ^2 test. Those variables presenting a descriptive level on the χ^2 test of less than or equal to 0.15 were