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ORIGINAL ARTICLE

Correlation of Hypocalcemia with Serum Parathyroid Hormone and Calcitonin Levels in Pediatric Intensive Care Unit

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Abstract
Objectives To investigate factors involved in causing hypocalcemia in critically ill patients.
Methods The patients aged 1 mo to 18 y, admitted to PICU at Nemazee Hospital, from May through November 2012, were reviewed. Those with impaired calcium hemostasis or on vitamin-D supplement were excluded. Calcitonin and parathyroid hormone levels were checked if ionized calcium level was less than 3.2 mg/d. Patient's demographic data, length of stay, Pediatric Risk of Mortality–III (PRISM-III) score, the need for mechanical ventilation, inotropic drug administration and outcome were recorded.
Results Among the 294 patients enrolled in the study, the incidence of ionized hypocalcemia was 20.4 %. The mortality rate was 45 % in hypocalcemic groups and 24.8 % in normocalcemic patients. Highly significant negative correlations were found between serum ionized calcium, PRISM-III score ($r=-0.371$, $P=0.004$), and calcitonin level ($r=-0.256$, $P=0.049$), but no significant correlation between hypocalcemia and parathyroid hormone level ($P=0.206$) was found. A significant difference was observed between survivor and non-survivor groups regarding PRISM-III score ($P=0.00$), ionized calcium ($P=0.00$), and calcitonin ($P=0.022$) but not parathyroid hormone level ($P=0.206$).
Conclusions Hypocalcemia was associated with increased mortality rate in PICU patients. A negative correlation was found between ionized calcium level and calcitonin. There was also a link between PTH level and severity of illness. It can therefore be concluded that evaluating serum ionized calcium, calcitonin, and PTH levels can be used as prognostic factors in critically ill patients.

Keywords Hypocalcemia · Pediatric intensive care unit · Parathyroid hormone · Calcitonin · Pediatric risk of mortality

Introduction

Hypocalcemia is a relatively common finding in critically ill patients. The incidence of ionized hypocalcemia has been reported as high as 54 % in adult intensive care units (ICU) [1]. The risk is also high in neonatal ICU, but the data from pediatric intensive care units (PICU) are limited. Some reports indicate a link between hypocalcemia and severity of illness [1–4]. However, such a relationship is not yet well established. The cause of hypocalcemia is multi-factorial including changes in calcium binding due to alteration in serum pH, protein and fatty acid levels, hypomagnesemia, hypophosphatemia, and renal failure [1]. These causative factors are very common in ICU settings.

Impaired calcium homeostasis, due to alteration in parathyroid hormone (PTH) level and calcitonin level can also be mentioned as the pathogenesis of decreasing serum calcium [2, 3]. Suppressed PTH level and high calcitonin level are

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demonstrated along with low serum calcium level in critically ill patients like sepsis and toxic shock, although the respective mechanism is not completely defined [2].

The aim of the present study was to investigate the incidence of hypocalcemia in critically ill patients at the time of, and throughout their admissions, and its correlation with mortality and illness severity as estimated by PRISM-III score in PICU. Also, the correlation between PTH level and calcitonin level with calcium has been evaluated.

Material and Methods

The study was conducted in the 10-beded medical PICU at Nemazee Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, from May through October 2012. The study group comprised patients aged 1 mo to 18 y, admitted to PICU, who stayed in the unit for more than 8 h, without pre-existing or known impaired calcium homeostasis (renal or liver failure and rickets, and parathyroid diseases), and not on vitamin-D supplement. Those with repeated hypocalcemia were excluded from the study. Venous blood samples were collected on admission and (or based on patient's condition) on alternate days until the acute phase of illness was over, and they were checked for BUN, Cr, Na, K, Mg, Ca and albumin. If total calcium was less than 8.5 mg/dl, ionized calcium (iCa) level and pH were checked on heparinized arterial blood. Serum calcitonin level and PTH level were determined if iCa level was less than 3.2 mg/dl. Information regarding demographic data, primary PICU diagnosis, PICU length of stay, PRISM-III score, the need for mechanical ventilation, inotropic drug administration and outcome were recorded. The study was approved by the ethics committee of the University. Because all measurements were performed as part of the routine metabolic evaluation of the patients, and confidentiality was maintained, the requirement for informed consent was waived, but written consents were obtained from parents or patients when PTH and calcitonin were needed to be measured.

Total calcium was measured by Methyl Timolol Blue (MTB) method in venous blood and iCa by OPH CCA-TS blood gas machine on heparinized blood. Serum level of PTH was estimated by Immuno Radio Metric Assay (IRMA) technique using Imunotech SAS kit (France), and calcitonin by Enzyme Linked Immuno-sorbant Assay (ELISA) using DIA Source Immuno assay S.A kit (Belgium).

Data analysis was performed using SPSS 18 software. Comparison of data was performed by Student's t-test for continuous variables and chi-square for discrete ones. A p-value less than 0.05 was considered significant.

Results

During the 6 mo period, 294 patients consisting of 138 (46.9 %) females and 156 males (53.1 %) were enrolled in the study. Hypercalcemia was not detected in any of the patients. The incidence of total hypocalcemia was 52.1 % (155) and ionized hypocalcemia was 20.4 % (60) either on or during admission. The median age of the patients was 2 y for both hypocalcemic and normocalcemic groups (P=0.005). The diagnoses included neurologic diseases (25.5 %), infectious diseases (22.4 %), respiratory illnesses (21.3 %), poisoning and drug overdoses (9.9 %), cardiac problems (8.5 %), gastroenterology diseases (5.8 %), and metabolic disorders (4.8 %). The same frequency of diseases was found in both groups with low and normal serum calcium levels (Table 1). The mean length of PICU admission was 12±4.7 d in survivors with hypocalcemia, compared with 2±1.2 d in the group with normal serum calcium (P=0.00).

The PICU mortality rate was 28.9 % (85 out of 294) which was 45 % in patients with low serum iCa level, compared to 24.8 % in patients with normal iCa level (P=0.002). There was no significant difference between patients with normal and low serum iCa regarding their need for inotropic agents (P=0.076), nevertheless, hypocalcemic patients required more ventilator support (P=0.014) (Table 2).

PTH level was within normal range in 37 (61.7 %), high in 21 (35 %) and low in 2 (3.2 %) of the patients with hypocalcemia on or during admission. Also, calcitonin was in normal range in 46 (76.7 %) and high in 14 (23.3 %) patients. Highly significant negative correlation was found between iCa level, PRISM-III (r=−0.371, P=0.004) and calcitonin levels (r=−0.256, P=0.049) in patients with hypocalcemia. However, iCa level showed no significant correlation with magnesium (P=0.361), albumin (P=0.401), and serum pH (P=0.368). Partial correlation between serum calcitonin and iCa in the presence of PRISM-III score as an independent value, was found insignificant (partial correlation=0.155, P=0.24), (Table 3).

Table 1 The frequency (number & percent) of admission diagnoses in hypocalcemic and normocalcemic patients in PICU

	Neurologic	Respiratory	Cardiac	GI	Infectious	Endocrine	Poisoning	Total
Hypocalcemic Group	16 (26.7 %)	17 (28.3 %)	3 (5 %)	2(3.3 %)	16 (26.7 %)	2 (3.3 %)	4(6.7 %)	60(100 %)
Normocalcemic Group	59 (25.2 %)	51 (21.8 %)	22 (9.4 %)	15(6.4 %)	50 (21.4 %)	2 (5.1 %)	25 (10.7 %)	234(100 %)
Total	75 (25.5 %)	68 (21.3 %)	25 (8.5 %)	17(5.8 %)	66 (22.4 %)	14 (4.8 %)	29 (9.9 %)	294(100 %)

Table 2 Demographic characteristics of the studied population in PICU

	Hypocalcemic No. (%)	Normocalcemic No. (%)	Total
Sex			
Male	32 (53.3)	124 (53)	156 (53.1)
Female	28 (46.7)	110 (47)	138 (46.9)
Survival			
Non-survivors	27 (45)	58 (24.8)	85 (29)
Survivors	33 (55)	176 (75.2)	209 (71)
Mechanical ventilation			
Yes	45 (75)	135 (57.5)	180 (61)
No	15 (25)	99 (42.3)	114 (39)
Inotropic support			
Yes	16 (26.7)	39 (16.7)	55 (19)
No	44 (73.3)	195 (83.3)	239 (81)
Total	60 (20.4)	234 (79.6)	294 (100)

There was no significant correlation between iCa and PTH levels (r=−0.04, P=0.716), but a positive correlation was found between PRISM-III score and serum PTH level (r=0.291, P=0.024). A significant difference was observed between survivor and non-survivor groups regarding PRISM-III score (P=0.00), iCa (P=0.00), and calcitonin (P=0.022), but not PTH level (P=0.206) (Table 4).

Discussion

The present study showed a high incidence of total and ionized hypocalcemia in critically ill patients (52.1 % and 20.4 %). The incidence of total hypocalcemia was 43.9 % in a previous study in 2009 in the same PICU [5]. Total hypocalcemia has been reported in 49 %- 90 % of ICU patients and ionized hypocalcemia between 15 and 50 % from different centers [1, 6]. The high incidence of hypocalcemia in this study is similar to previous studies and shows the importance of a common issue in PICU.

Table 3 Correlation between serum iCa, PRISM-III and other measured parameters in PICU patients

	Ionized Ca	PRISM-III
Ionized Ca (Hypocalcemia <3.2 mmol/L)	–	r=−0.371 P=0.004
Mg (Hypomagnesemia <1.5 mmol/L)	r=0.12 P=0.361	–
PTH (NL=10–65 pg/ml)	r=−0.04 P=0.716	r=0.291 P=0.024
Calcitonin (NL<11 pg/ml)	r=−0.256 P=0.049	r=0.321 P=0.012
Albumin (NL=3.5–5 g/dl)	r=−0.111 P=0.401	–
pH (NL=7.35–7.45)	r=0.118 P=0.368	–

NL Normal levels

Table 4 PRISM III score, iCa, PTH and calcitonin levels in survivors and non-survivors groups in PICU patients

	PRISM-III	Ionized Ca (mmol/L)	PTH (pg/ml)	Calcitonin (pg/ml)
Survivors (Mean±SD)	17±4.21	2.2±0.55	66.35±66.46	6.31±5.16
Non- survivors (Mean±SD)	27.85±6.4	1.69±0.30	94.55±10.48	9.85±9
r	−7.871	4.343	−1.278	−2.305
p	0.000	0.000	0.206	0.022

It was observed that hypocalcemia was associated with increased mortality rate and length of PICU stay. This relation has been demonstrated in previous studies in adults and children as well [1–4]. Whether the hypocalcemia has a direct impact on survival, or it is just a marker of serious illness, needs to be investigated. Although some studies have shown no independent correlation with ionized calcium level and hospital or ICU mortality [7].

In the present study there was a significant correlation between hypocalcemia and the number of patients who needed ventilator but not inotropic support. However, in the previous study it was observed that hypocalcemic patients needed more inotropic agents' support, which is reasonable [5]. It is recommended that hypocalcemia is considered in any hypotensive patient refractory to fluid and inotropes [4]. It seems that the lack of a uniform guideline for starting inotropic agents could be responsible for such a difference in the results. This fact emphasizes the use of sepsis guideline in resource-limited countries [8]. The most common primary diagnosis, among hypocalcemic patients was found to be respiratory, followed by neurologic and infectious diseases. This is inconsistent with other observations in which sepsis and septic shock were the most common diagnosis [4, 5, 9]. However, in some studies it has been revealed that hypocalcemia correlates with the severity of illness rather than the type of primary diagnosis. It appears that similar frequencies of hypocalcemia from various ICU settings suggest a shared disease mechanism rather than a specific disease entity [1–4].

Hypomagnesemia can contribute to hypocalcemia by decreasing the PTH secretion and causing end-organ resistance. It is suggested that decreased serum magnesium should be considered as a cause in any hypocalcemic patient resistant to treatment [1, 10, 11]. However, no association was found between hypomagnesemia and hypocalcemia in the index study. Although some researchers reported significant correlation between iCa and pH, albumin, and magnesium, the

correlation in the index study was weak and could be ignored [7].

A significant negative correlation was found between iCa and calcitonin level (r=−0.256, P=0.049). This has been described by other authors as well [2, 12, 13]. Also, a significant positive correlation was found between PRISM-III score and calcitonin level (r=0.321, P=0.012). This indicates that serum calcitonin level increases as the severity of the disease progresses. The authors calculated partial correlation between iCa and calcitonin with control of PRISM-III score, and to their surprise, this time the correlation was not significant (partial r=−0.155, P=0.24). So, the authors could conclude that decreased iCa does not directly increase calcitonin level. It may worsen the severity of the patient's condition, which, in turn, leads to rising serum calcitonin level. This was explained from the presence of inflammatory cytokines such as interleukine-1, tumor necrosis factor-alfa and calcitonin precursors which are secreted during the acute phase of diseases [14]. A previous finding that reported increased serum procalcitonin had correlation with the disease's severity could serve as an explanation for the index result [15].

The present study showed no correlation between serum PTH level and iCa, but revealed a significant direct association with disease severity score. PTH is the most important factor in the calcium homeostasis. It was supposed that suppression of PTH causes hypocalcemia in critically ill patients, but data demonstrates high PTH level in hypocalcemic patients, which can be due to end organ resistance [2]. Although in this study it was found that PTH level was high in patients with high PRISM-III score, no association was demonstrated between serum calcium and PTH level. The data indicates the need for further investigation into the above-mentioned issue in critically ill patients.

Although the authors could not find a significant correlation between survivors and non-survivors in terms of PTH level, it was showed that mean iCa level, PRISM-III score and calcitonin level were significantly different between these two groups. This fact highlights the importance of determination of iCa and calcitonin level in critically ill patients as a risk factor associated with mortality [16].

As vitamin D is one of the important factors in calcium homeostasis, its level needs to be evaluated in hypocalcemic patients. More accurate result would be achieved if measuring Vitamin D level was available in authors' centre.

Conclusions

Hypocalcemia is a common finding in PICU patients. It is associated with increased risk of mortality and length of ICU stay. Lower calcium level is associated with higher calcitonin level and severity of illness. There is also a link between PTH level and severity of illness. Thus, evaluating the calcium and calcitonin levels can be used as a prognostic factor in critically ill patients in PICU.

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Conflict of Interest None.

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