Hypocalcemia in critically ill hospitalized patients

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ABSTRACT

Background: Hypocalcemia is frequently encountered in critically ill hospitalized patients. The most accurate measure of true hypocalcemia is ionized calcium level. This study was done to ascertain the frequency, risk factors and outcome in critically ill patients admitted to the ICU with hypocalcemia.

Materials and Methods: This was a prospective study of a series of ICU patients during a 6-month period. For the purpose of the present study, hypocalcemia was defined as ionized Calcium (iCa^{++}) level less than 1.16 mmol/L. The patients were divided into two groups: hypocalcemic (iCa^{++} level < 1.16 mmol/l) and normocalcemic (iCa^{++} level between 1.16–1.33 mmol/L). Both these groups were compared using the log-rank test, and the results are presented as Kaplan–Meier curves. Hazard ratios for death from hypocalcemia were calculated by logistic regression model.

Results: Of the 279 patients, 200 (71%) were hypocalcemic and 79 (29%) were normocalcemic (incidence ratio 2.53, 95% confidence interval 1.95 to 3.32, p value< 0.0001). The hypocalcemic group had significantly lower ionized Ca^{++} levels and higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score when compared to those of the normocalcemic group (p< 0.001). Patients with severe sepsis, trauma, APACHE II score greater than 25, renal failure patients requiring renal replacement therapy and those who had undergone emergency surgery were more likely to have low serum ionized Ca^{++} (p< 0.05). Patients with low serum ionized Ca^{++} values spent a longer time in the ICU (p = 0.02) and had an increased mortality rate (hazard ratio = 2.23; 95% confidence interval of ratio = 1.323 to 3.773, P = 0.0145), than patients in the normocalcemic group.

Conclusions: Ionized hypocalcemia is frequent in critically ill patients. Severe sepsis, trauma, APACHE II score > 25, emergency surgery and renal failure are predisposing factors. Patients with low serum ionized Ca++ values had longer ICU stay and longer mechanical ventilation days, with a higher mortality rate.

Key words: hypocalcemia, serum calcium level, critically ill patients

INTRODUCTION

Ionized calcium should be measured when the diagnosis of hypocalcemia is considered in critical illness, as albumin adjusted serum calcium is not suitable for diagnosis of hypocalcemia in critical illness.[1,2] Hypocalcemia is frequently encountered in critically ill hospitalized patients.[3] It is defined as a reduction in ionized serum calcium (Ca) concentration below 1.16mmol/l.[4] The frequency of hypocalcemia in intensive care unit (ICU) patients ranges from 65 to 88%.[5] It is associated with increased disease severity as measured by Acute Physiology And Chronic Health (APACHE) II score and poor outcome, however, attributable mortality is not established.[6,7] Severe hypocalcemia can cause laryngeal spasm, carpopedal spasm, bronchospasm, seizures, and even respiratory arrest. Mental changes include irritability, depression, and decreased cognitive capacity. The electrocardiogram may show shortening of the QT interval and arrhythmias. Overt heart failure is seen rarely.[8] The causes of hypocalcemia in critically ill patients include impaired PTH secretion or action, vitamin D deficiency or resistance, calcium chelation/ precipitation and impaired mobilization from bones.[9,10,11]

The present study was intended to study the frequency of hypocalcemia, correlation with disease severity as measured by APACHE- II score and outcome in critically ill patients admitted to the ICU of a teaching medical college of eastern Orissa, India.

MATERIAL AND METHODS

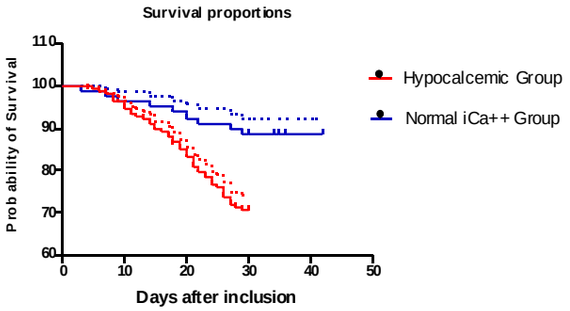
This was an observational, prospective study of a series of ICU patients during a 6-month period (June 2011 to November 2011). Patients with hypercalcemia and hypomagnesemia were excluded. Hypocalcemia was defined as an ionized Ca level less than 1.16 mmol/L. The normal range for our institution is 1.16–1.33 mmol/L. To determine frequency of hypocalcemia, patients were considered hypocalcemic if they had ionized Ca level less than 1.16 mmol/L at any time a measurement was available during admission to the ICU for all the groups. The patients were divided into two groups: hypocalcemic (iCa^{++} level < 1.16 mmol/l) and normocalcemic groups (iCa^{++} 1.16–1.33 mmol/L). Patient characteristics include age, sex, admitting diagnosis and pre-existent chronic diseases. Parameters for patients included mean arterial pressure, presence of acute renal failure (ARF) and need for renal replacement therapy, need for mechanical ventilator and ventilator days, duration of ICU and hospital stay (days) were recorded as observational data and other variables useful to calculate APACHE-II and the Sequential Organ Failure Assessment (SOFA) scores.[12]

Laboratory data included values for total serum calcium (Ca), ionized serum Ca, magnesium (Mg), phosphate, creatinine, albumin and arterial pH. Calcium was analyzed with an ionic-specific electrode (Cobas b 121 POC system blood gas analyzer) using arterial blood sample. For analysis, pH 7.4 corrected values were used.

Statistical analysis

The discriminative powers of admission and lowest ionized calcium values regarding day-30 mortality were evaluated by producing receiver operating curves (ROC). Binary end points were analyzed by means of a Fisher's exact test. Continuous variables were compared with the use of unpaired t-tests, Welch's tests, or Wilcoxon ranksum tests. All odds ratios and their corresponding 95% confidence intervals were calculated according to the profile-likelihood method. The time from inclusion to death in the two groups was compared with the use of the log-rank test, and the results are presented as Kaplan–Meier curves. Hazard ratios for death from hypocalcemia were calculated by logistic regression model. All p values were 2-tailed and p values of < 0.05 were considered statistically significant.

Figure 1. The time from inclusion to death in the two groups



RESULTS

During the study period, 319 patients were admitted to the ICU, of whom 279 were included and rest were excluded as per exclusion criteria. Of these 279 patients, 200 (71%) were hypocalcemic and 79 (29 %) were normocalcemic (incidence ratio 2.53, 95% confidence interval 1.95 to 3.32, p value < 0.01). The hypocalcemic group had significantly lower ionized Ca^{++} levels and higher APACHE II score when compared to those of the normocalcemic group (p < 0.01). Patients with severe sepsis, trauma, APACHE-II score greater than 25, renal failure patients requiring renal replacement therapy and those who had undergone emergency surgery were more likely to have low serum ionized Ca++ (p < 0.05). Patients with low serum ionized Ca++ values spent a longer time in the ICU (p = 0.02) and had an increased mortality rate (hazard ratio = 2.23; 95% confidence interval of ratio = 1.323 to 3.773, P = 0.01), than patients in the normocalcemic group.

Table 1. Baseline Characteristics of the Study Patients

Variable	*Hypocalcemia group (ionized calcium [Ca] < 1.16 mmol/L)*	*Normocalcemia group*	
Age — yr	60.4±17.2	59.9±17.1	
Female sex — no./total no. (%)	74/200 (37)	27/79 (34.1)	
Weight — kg	63.91±15.1	65.21±14.7	
Body-mass index	27.9±7.7	28.0±7.2	
Interval from ICU admission to ionized calcium estimation — hr	3.4±1.4	3.4±1.3	
Reason for ICU admission — no./total no. (%)			
Operative	70/200 (35)	7/79 (8.8)	
Nonoperative	130/200 (65)	72/79 (91.2)	
Location before ICU admission — no./total no. (%)			
Emergency department	46/200 (23)	7/79 (8.87)	
Hospital floor (or ward)			
Without previous ICU admission	42/200 (21)	49/79 (62)	
With previous ICU admission	4/200 (2)	1/79 (1.27)	
Another ICU	8/200 (4)	2/79 (2.53)	
Another hospital	30/200 (15)	13/79 (16.45)	
Operating room			
After emergency surgery	46/200 (23)	3/79 (3.79)	
After elective surgery	24/200 (12)	4/79 (5.06)	
APACHE II score	27±8.98	22±7.68 (P < 0.01) Wilcoxon test	
Ionized Calcium level —mmol/L	0.84±0.23	1.26±0.15 (P < 0.01) Wilcoxon test	
Organ failure or dysfunction — no./total no. (%)			
Respiratory			
Dysfunction (SOFA score, 1–2)	80/200 (40)	24/79 (39.2)	
Failure (SOFA score, 3–4)	94/200 (47)	37/79 (46.8)	
Coagulatory			
Dysfunction (SOFA score, 1–2)	46/200 (23)	12/79 (15.1)	
Failure (SOFA score, 3–4)	8/200 (4)	2/79 (2.6)	
Hepatic			
Dysfunction (SOFA score, 1–2)	58/200 (29)	22/79 (27.8)	
Failure (SOFA score, 3–4)			
Cardiovascular			
Dysfunction (SOFA score, 1–2)	38/200 (19)	15/79 (18.8)	
Failure (SOFA score, 3–4)	118/200 (59)	45/79 (56.7)	
Renal			
Dysfunction (SOFA score, 1–2)	70/200 (35)	25/79 (31.6)	
Failure (SOFA score, 3–4)	38 /200 (19)	7/79 (8.8)	
Renal-replacement therapy — no./total no. (%)	38 /200 (19)	7/79 (8.8)	
Mechanical ventilation — no./total no. (%)	47/100 (47)	37/79 (46.8)	
Subgroup classification — no./total no. (%)			Pvalue
Severe sepsis at admission	112/200 (56)	13/79 (16.45)	<0.01
Trauma	54/200 (27)	7/79 (8.86)	0.05
APACHE II score ≥25	150/200 (75)	24/79 (30.37)	0.01
Surgery			
After emergency surgery	46/200 (23)	3/79 (3.79)	0.01

* Plus–minus values are means ± SD. APACHE II scores can range from 0 to 71, with higher scores indicating more severe illness, and SOFA scores can range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction. Severe sepsis was defined as per the criteria of the American College of Chest Physicians Society of Critical Care Medicine.[12]

Table 2. Outcomes and Adverse Events

Outcome Measure	Hypocalcemia group (n=200) (ionized calcium [Ca] < 1.16 mmol/L)	Normocalcemia group (n=79)	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%) ; all cause 30-day	58/200 (29)	9/79 (11.3)	0.39 (0.18 to0.83)	Logistic regression	0.01
Days in ICU — median (IQR)	16 (16 to 20)	14 (12 to 16)	0	Log-rank test	0.02
Days in hospital — median (IQR)	23 (15 to 23.5)	21 (14 to 23)	0	Log-rank test	0.15
Mechanical ventilation — no. of patients/ total no. (%)	94/200 (47)	37/79 (46.8)	0.99 (0.62 to1.58)	Pearson's test	0.98
Days of mechanical ventilation	6.91±2.87	6.6±3.1	0	Wilcoxon rank-sum test	0.46
Renal-replacement therapy — no. of patients/ total no. (%)	38 /200 (19)	5/79 (6.3)	0.33 (0.12 to0.87)	Pearson's test	0.03
Days of renal - replacement therapy	0.8 ±2.3	0.7 ± 2.1	0	Wilcoxon rank-sum test	0.34

* Plus–minus values are means ± SD. CPR denotes cardiopulmonary resuscitation, and IQR inter quartile range.
† Absolute differences (percentage points) are given for median days in the ICU or hospital, and mean ± SD days of mechanical ventilation or renal-replacement therapy; for all other measures, odds ratios are given.
‡ Organ failure was defined as a SOFA score of 3 or 4 for any individual organ system.

DISCUSSION

The frequency of hypocalcemia in ICU patients ranges from 65 to 88%.[5] Results of our study showed that hypocalcemia is very common in critically ill patients (as high as 71% in our cohort). Risk factors for hypocalcemia included severe sepsis, trauma, renal failure patients and those who had undergone emergency surgery. Chernow et al., had identified sepsis, renal failure and postabdominal surgery as risk factors for hypocalcemia.[3] Zaloga et al., found ionized hypocalcemia in 30% of cases of Gram-negative sepsis and in none of those cases of sepsis caused by Gram-positive bacteria.[13] In a study by Vivien B (2005) hypocalcemia is frequently seen in severe trauma patients, and colloid-induced hemodilution and severe shock and ischemia-reperfusion appear to be important causative factors.[14] In our study the hypocalcemic group had significantly lower ionized Ca^{++} levels and higher APACHE II score when compared to those of the normocalcemic group ($p < 0.01$). Patients with low serum ionized Ca^{++} values spent a longer time in the ICU ($p = 0.02$) and had an increased mortality rate (hazard ratio = 2.23; 95% confidence interval of ratio = 1.323 to 3.773, P = 0.01), than patients in the normocalcemic group. Similar correlation was also addressed in a study done on critically ill patients by Zivin et al.[5]

CONCLUSION

Ionized hypocalcemia is a frequent finding in critically ill patients. Severe sepsis, trauma, APACHE II score > 25, emergency surgery and renal failure are predisposing factors for hypocalcemia. Patients with low serum ionized Ca++ values had longer ICU stay and longer mechanical ventilation days (p=0.03). Patients with ionized hypocalcemia have

a higher mortality rate than those with normocalcemia; however, because the former are more severely ill, no causality is apparent or suggested.

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