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Research Article

HYPOCALCEMIA IN CRITICALLY ILL PATIENTS IN A TERITIARY CARE HOSPITAL

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A B S T R A C T

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 single- centre, retrospective, observational study. The population was derived patients admitted to the ICU, the postoperative critical care unit or the high dependency unit at SMHS Hospital were eligible for inclusion. 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 <1.16mmol/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.

Results: Of the 170 patients, The mean age of patients admitted was 59.5yrs, with a median of 61yrs. Out of these, 47% were females and 53% male and the mean APACHE score of 19(IQR 14-24). We measured total calcium, albumin corrected calcium and ionised calcium in our study, after an initial assessment. The mean total calcium levels were 8.8g/dl and the mean corrected calcium (corrected for hypoalbuminemia) level 9.2mg/dl. Out of these 47% patients were hypocalcemic (S Ca <8.8mg/dl), 50.1%patients were normocalcemic and 5 patients (2.9%) were hypercalcemic which were excluded from further analysis. Further, the mean admission iCa was 4.2mg/dL (SD) and 88.2% patients were classified as hypocalcemic (iCa <4.7mg/dl). Out of the 85 patients who were normocalcemic on serum calcium measurements 65(76.5%) were hypocalcemic when ionised calcium was measured. Patients with low serum ionized Ca++ values had longer ICU stay and longer mechanical ventilation days, with a higher mortality rate. Conclusion hypocalcemia is usual finding in critically ill patients, and has an adverse effect on disease severity and outcome and also the hospital stay.

INTRODUCTION

Hypocalcemia is a common derangement in both medical and surgical patients requiring intensive care. The first clinical observations and studies in hypocalcemic critically ill patients date back to the early 70's and 80's of the last century [1,2]. The incidence of hypocalcemia in critically ill patients varies widely depending on the different underlying diseases and comorbidity. In an analysis of 12 studies performed between 1988 and 2014 Aberegg believes the incidence of hypocalcemia in critically ill patients ranges from 50-88% [3]. The reported prevalence varies significantly between studies due to differences in the population studied and the cutoff values used, with published figures ranging from 15% to 88%.[4,5]

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Hypocalcemia is thought to be caused by the following mechanisms: i) increased fecal and/or urinary excretory Ca2+ losses in the presence of fixed dietary Ca2+ intake; ii) catecholamine-mediated translocation of plasma Ca2+ into tissues; and iii)reduced dietary Ca2+, often in association with vitamin D deficiency.[6] Most common causes of hypocalcemia include trauma, acute and chronic renal failure, sepsis, hypoparathyroidism, hypomagnesemia, vitamin D deficiency, and complexing with citrate, albumin, or infused phosphate. Dilution of plasma induced by administration of massive amounts of intravenous fluid in a resuscitative effort is reported to be an important cause of hypocalcemia in trauma patients.[7]

Decreased bone resorption, calcium chelation, calcitriol deficiency, decreased secretion or action of parathyroid hormone with or without hypomagnesemia, and increased urinary calcium excretion contribute to drug-induced hypocalcemia.[8] Spuriously low concentration of calcium can

be detected following the administration of gadolinium-based contrast, as gadolinium interferes with calorimetric-based calcium assays, while ionised calcium concentration measurements remain unaffected. [9]

In this population, however, the diagnosis of hypocalcemia is complicated by limitations in the 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 ionised calcium can be critical in determining an individual's true serum calcium status.[10]

Aims and objectives

Our study aims to study the critically ill patients and determine their total, albumin corrected as well as ionised calcium and determine the prevalence of hypocalcemia in this population as well as the effect of hypocalcemia on in hospital stay and mortality in these patients.

MATERIALS AND METHODS

This was a single- centre, retrospective, observational study. The population was derived patients admitted to the ICU, the postoperative critical care unit or the high dependency unit at SMHS Hospital were eligible for inclusion. Ethical approval was obtained from the Research Ethics Committee and consent was obtained from all participants. Patients were excluded if valid consent could not be obtained. Admission details, demographic information and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were collected and patients followed up to determine 28-day mortality. Daily assessment of the clinical progress of the patients was noted. All blood tests were carried out as part of routine clinical practice and consisted of daily serum chemistry and 4-hourly blood gas analysis unless otherwise dictated by clinical need.

Admission serum biochemistry and blood gas results (defined as the first available results within 24 h of the recorded admission date) were extracted alongside the serum biochemistry and blood gas results at 6 am (+/- 2 hours). Ionised calcium (iCa), pH and lactate results were obtained from blood gas analysis on whole arterial blood collected in heparinised syringes. Measurements were carried out by trained staff on a RapidLab 1265 blood gas analyser (Siemens Healthcare Diagnostics, Inc.) based on the ICU. iCa was not adjusted for pH. Sodium and potassium were measured using ion-selective electrodes using the Roche/Hitachi cobas 8000 ISE analyser module in the central hospital laboratory. Total calcium, magnesium, phosphate and albumin measurements were carried out with dye-forming reactions detected photometrically using the Roche/Hitachi cobas c701 analyser module in the central hospital laboratory All statistical analysis was performed using SPSS version 21 for Windows (IBM). Patients hypercalcemic on admission were excluded from analyses. Continuous data were assessed for normality visually by plotting histograms. For normally distributed data the mean (standard deviation) and parametric tests were used and for non normally distributed data the median (interquartile range (IQR)) and non-parametric tests were used. Categorical data, quoted as n (%), were assessed using cross-tabulation and the chi squared test for independence. A P value < 0.01 was taken to be statistically significant.

RESULTS

Our study was conducted in a tertiary care centre and data from 170 patients admitted in the ICU was available for inclusion in the study. The mean age of patients admitted was 59.5yrs, with a median of 61yrs .Out of these, 47% were females and 53% male and the mean APACHE score of 19(IQR 14-24). The baseline variables of study group is shown in table 1.

Table 1 Baseline variables for all patients and for those normocalcemic and hypocalcemic

Variable	All patients	Normocalcaemic (n=85)	Hypocalcaemic (n=80)	P value
Age(yrs)	59.5(48-70)	61(49-74)	62(48-77)	0.88
Male sex	90(53%)	50(59%)	35(41%)	0.33
Apache II score	17(13-22)	17(13-22)	19(14-23)	0.17
Length of stay (days)	8(4-14)	8(4-14)	12(6-19)	<0.001
pH	7.38(7.29-7.44)	7.38(7.3-7.44)	7.37(7.3-7.43)	0.55
Sodium	139(135-142)	139(135-142)	138(134-143	0.016
Potassium	4.3(3.8-4.6)	4.3(3.8-4.6)	4.2(3.8-4.7)	0.6
Lactate	1.5(1-2.5)	1.5(1-2.3)	1.8(1-2.8)	<0.001
Albumin	25(19-31)	26(19-31)	21(18-26)	<0.001

Multivariate logistic analysis for biochemical abnormalities with hypocalcemia was done and results are shown in table 2.

Table 2 multivariate logistic regression of biochemical variables with hypocalcemia

Variable	Odds ratio (OR , 95%CI)	p value
APACHE II	1.00(0.99-1.03	0.67
Sodium	0.99(0.95-0.99)	0.03
Magnesium	0.39(0.16-0.77)	0.022
Lactate	1.12(1.04-1.3)	0.006
Albumin	0.93(0.91-0.94)	<0.001

Correlation of different indices of calcium and disease severity shown in table 3

Table 3 Pearson correlation of calcium and disease severity

Variable	Total calcium	Ionised calcium	Corrected calcium	APACHE
Total calcium		p<0.001 ar= 0.316	p<0.001 ar= 0.465	p<0.001 ar=0.365
Ionised calcium	p<0.001 ar=0.416		p=0.116 ar=0.043	p<0.001 ar=0.699
Corrected calcium	p<0.001 ar=0.447	p=0.853 ar=0.011		p=0.04 ar=0.323

DISCUSSION

Hypocalcemia is a common derangement in both medical and surgical patients requiring intensive care. The incidence of hypocalcemia in critically ill patients varies widely depending on the different underlying diseases and comorbidity. In our study of 170 patients admitted in the ICU over a period of 6months with a median APACHE score of 19, the incidence of hypocalcemia was 47% when total calcium was measured and its increased to 88.2% when ionised calcium was measured Similarly in an analysis of 12 studies performed between 1988 and 2014 Aberegg believes the incidence of hypocalcemia in critically ill patients ranges from 50-88% [3].

However the measurement of calcium in these patients poses certain challenges. Some studies have used corrected calcium values while others measured ionised calcium. It is also not clear if the calcium measurements were made for diagnostic, screening, homeostatic or daily routine purposes. The only

thing that is evident at present is that some 50% of critically ill patients in an ICU will have hypocalcemia at some moment at some day during their stay[3].

We measured total calcium, albumin corrected calcium and ionised calcium in our study, after an initial assessment. The mean total calcium levels were 8.8g/dl and the mean corrected calcium (corrected for hypoalbuminemia) level 9.2mg/dl. Out of these 47% patients were hypocalcemic (S Ca <8.8mg/dl), 50.1%patients were normocalcemic and 5 patients (2.9%) were hypercalcemic which were excluded from further analysis. Further, the mean admission iCa was 4.2mg/dL (SD) and 88.2% patients were classified as hypocalcemic (iCa <4.7mg/dl). Out of the 85 patients who were normocalcemic on serum calcium measurements, 65(76.5%) were hypocalcemic when ionised calcium was measured. In our study an important observation was made that hypocalcemia remains under-diagnosed when the total calcium is measured but when the ionised calcium is considered the patients being diagnosed as hypocalcemic significantly increases as Also seen by Matthew C. Byrnes *et al* [11] the reason behind this disparity is that total calcium is usually dependent on albumin levels and many other factors and in critically ill patients we usually observe a derangement in these factors along with albumin, being an acute phase reactant. other factors and mechanisms shown as cause for hypocalcemia in critically ill patients, such as pro-inflammatory biomarkers [3], end organ resistance to PTH, extra and intra cellular redistribution of calcium ion, suppression of PTH secretion, and catecholamine release in critically ill patients[4] in our study we observed significant inverse association between total, ionised, and corrected calcium concentrations with disease severity. although more significant association was seen in ionised calcium and disease severity, as supported by study done by Slomp *et al*[12]. hence our study gives a important clue that in critically ill patients ionised calcium should be measured and considered as a standard method, as also recommended by Calvi *et al*[13]. One more observation which was seen in our study was that patients with low ionised calcium had longer stay of admission in hospital and the finding was statistically significant and was seen more prominently in severely hypocalcemic patients as was also seen by Steele *et al* [14].

CONCLUSION AND RECOMMENDATION

1. Overall by analysis of clinical and biochemical database our study shows hypocalcemia is usual finding in critically ill patients , and has an adverse effect on disease severity ,the hospital stay and outcome.
2. Our study also concluded that total calcium measurement is not a reliable indicator of hypocalcemia as it needs albumin correction and is multivariate factor dependent in critically ill patients visaviz ionised calcium is a better and reliable biochemical marker and should be standard measurement tool of serum calcium.

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