IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 3 Ser.18 (March. 2023), PP 27-32
www.iosrjournals.org

Correlation of Admission Apache Ii Score and Hypocalcemia As A Severity Marker In Critically Ill Patients In Medical Intensive Care

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Abstract
Introduction*: Calcium is one of the crucial ions that has an immense role in maintainingbiological homeostasis. It's known that critical illness may trigger an acute phase response which may be associated with severe metabolic derangements including hypocalcemia. Various studies have shown that hypocalcemia is a common electrolyte imbalance in ICU patients and is associated withadverseprognosticoutcomes. APACHE- II score is commonly used to assess severity of critically ill patients but is cumbersome and involves multiple parameters of which calcium is not considered.*
Objectives*:The study aims to assess admission hypocalcemia as a severity marker in critically patients and its correlation with APACHE –II score.*
Methods*: This was a hospital based prospective observational study on 207 Medical ICUpatients over a period of 1 year. Ionized calcium values were obtained from blood gas analysis on whole arterial blood and admission APACHE II Score was calculated for all patients . Outcome data was compared using SPSS version 22.0 software.*
Results: *In our study, 105 patients (50.72%) were hypocalcemic. The severely hypocalcemic group had higher mean APACHE II score when compared with the normocalcemic group (21.68±2.60vs7.02±3.05,p<0.05),had longer stay in the ICU than the normocalcemic group (13.61 ± 4.49 days vs 6.58 ± 3.11 days, p<0.05) and had higher mortality rate (52.83 % vs 6.86%, p<0.001).The mean ionized calcium of the survivors and non-survivors in our study was 1.09±0.26 mmol/L and 0.79±0.23 mmol/L respectively and the difference was statistically significant (p<0.05). Hypocalcemia was most prevalent among sepsis patients(91.43%).*
Conclusion*: Hypocalcemia on admission is a frequent occurrence in ICU patients and severity of hypocalcemia had a positive correlation with higher APACHE II score in critically ill ICU patients.*

Key words: *Hypocalcemia, APACHE II, Sepsis*
Conflict of interest: *None*

Date of Submission: 15-03-2023 Date of Acceptance: 31-03-2023

I. Introduction

Hypocalcemia is a common derangement in both medical and surgical patients requiring intensive care. ICU patients are critically ill and multiple mechanisms are involved in the pathophysiology of hypocalcemia such as:

a) increased fecal and/or urinary excretory Ca2+ losses in the presence of fixed dietary Ca2+intake;
b) catecholamine – mediated translocation of plasma Ca2+ into tissues
c) reduced dietary Ca2+, often in association with vitamin D deficiency.[1]

In blood, total calcium concentration is normally 2.2- 2.6 mmol/l (8.5- 10.5mg/dl) of which about 50% is ionized. Hypocalcemia is defined as ionized serum calcium concentration below 1.12 mmol /l [2]. Alterations in serum protein concentrations directly affect the total blood calciumconcentration even if the ionized calcium concentration remains normal. Acidosis also alters ionized calcium by reducing its association with proteins. The best practice thus,is to measure blood ionized calcium directly.

APACHE II score has been used to assess the severity of ICU patients and involves measuring multiple parameters which may be difficult to estimate on admission into intensive care.

AIMS AND OBJECTIVES

To correlate the admission hypocalcemia with APACHE II score as a severity marker in patients admitted in medical intensive care with death as a primary end point.

II. Materials and Methods

The present study was conducted in the Intensive Care Unit of the Department of Medicine, Silchar Medical College & Hospital, Silchar, Assam. It was a hospital based prospective, observational and cross sectional study done for a period of one year.

Inclusion criteria

All patients admitted in the Intensive Care Unit of Medicine Department of Silchar Medical College and Hospital, during the study period were included in the study.

Exclusion criteria

1) Patients who are unwilling for investigations or from whom a valid consent could not be obtained
2) If patients were discharged, died or put on the care of dying pathway within the first 48 hours after admission.
3) Patients who had received multiple blood transfusions before sampling.
4) Patients on calcium and vitamin D therapy at the time of or before admission.
5) Patients on medications affecting serum calcium levels like furosemide, steroids, heparin, protamine, glucagon or phenytoin.
6) Patients with underlying chronic renal insufficiency and those on hemodialysis.
7) Patients suffering from acute pancreatitis, hyperbilirubinemia and hypomagnesaemia (<1.5mg/dl).

All selected patients were taken up for evaluation after obtaining valid consent. Detailed clinical history, general and systemic examination findings were recorded using a predesigned structured proforma.

Data on following information were extracted: age on ICU admission, sex, admission Acute Physiology and Chronic Health Evaluation Score II (APACHE II) score and calcium level estimation (day1), mortality during ICU stay, all measurements of serum ionized calcium during ICU stay. Co morbidities including hypertension, paralysis, chronic pulmonary disease, diabetes, renal failure,acquired immunodeficiency syndrome(AIDS), coagulopathy, obesity and weight loss were also extracted. An APACHE II score of 20 or more was considered high in the study.

The primary endpoint in the study was ICU mortality which was defined as death observed during ICU stay.

The secondary end points of the study were:

1) Prevalence of hypocalcemia in different diagnostic groups
2) Correlation of hypocalcemia with disease severity as assessed by APACHE II score
3) Length of ICU stay in days

The measurement was done routinely on all patients on admission and on a daily basis mostly in the morning hours (between 8am to 9am). Ionized calcium was measured on admission into ICU and was labeled as **Ca0**

The selected patients were subjected to detailed laboratory investigations and Arterial Blood Gas analysis. The serial number and hospital number of all patients were noted.

Ionized calcium results were obtained from blood gas analysis on whole arterial blood collected in lithium heparin vials . Measurements were carried out immediately by trained ICU staff on a blood gas analyzer RADIOMETER ABL80 FLEX in the Medical ICU. Ionized calcium levels adjusted for pH, was used for the study. The other laboratory tests were done at the Hematology, Microbiology and Biochemistry laboratories**.** The collected data was compiled, tabulated and analysed in terms of descriptive statistics using SPSS version 22.0 software. P<0.05 wasconsidered statisticallysignificant.

III. Results and observations:

A total of 207 ICU admissions satisfied the inclusion criterion and were included in the analysis. Hypocalcemia was considered if the calcium level was less than 1.1 mmol/L

Depending on theionized calcium levels,the study population was classified into the following groups.

1. Normocalcemia 1.1-1.35 mmol/L
2. Mild hypocalcemia 0.91-1.09mmol/L
3. Moderate hypocalcemia 0.81- 90 mmol/L
4. Severe hypocalcemia < 0.8mmol/L

Table 1 shows the prevalence of hypocalcemia on admission. Of the 207 cases, 105 patients (50.72%) had hypocalcemia on ICU admission, of which 53 patients (25.60 %) had severe hypocalcemia, 34 patients (16.43%) had moderate hypocalcemia and 18 patients (8.69%) had mild hypocalcemia.

Groups	**Number of patients**	**Percentage (%)**
Normocalcemia (1.1 - 1.35 mmol/L)	102	49.28
Mildhypocalcemia (0.91-1.09 mmol/L)	18	8.69
Moderatehypocalcemia (0.81-90 mol/L)	34	16.43
Severe hypocalcemia (<0.8 mmol/L)	53	25.60

Table 1: Prevalence of hypocalcemia among the study population

Table 2 depicts the base line characteristics between the different calcium groups. The mean age of patient population in our study was 55.35± 15.85 years. The mean age of the normocalcemic group was 55.24± 15.25 years; hypocalcemic group was 55.07 ± 16.53 years and the severely hypocalcemic group was 56.19 ± 18.56 years.

The prevalence of hypocalcemia among the different diagnostic groups has also been displayed in the table. 2

Variables	Normo-calcemia	Mild hypocalcemia	Moderate Hypocalcemia	Severe Hypocalcemia	P value
Age (years)	55.24±15.25	55.07±16.53	54.18±18.76	56.19±18.56	0.14
Prevalence of comorbid conditions among different groups(%)					
Sepsis	8.57	8.57	25.71	57.14	
Ischaemic stroke	56.52	8.7	8.7	26.09	
Hemorrhagic stroke	41.67	8.33	12.5	37.5	
Decompensated Cirrhosis	47.36	10.53	15.79	26.32	
Coronary artery disease	71.43	7.14	10.71	10.71	
Acute encephalitis	23.08	7.69	15.38	53.85	
Acute kidney injury	66.67	22.22	11.11	Nil	
Respiratory diseases (COPD/Pneumonia)	65.79	5.26	21.05	7.89	
Mean **APACHE II** Score	7.02±3.05	14.28±4.31	15.32±4.83	21.68±2.60	<0.05
Length of ICU stay(days)	6.58±3.11	11.83±4.09	12.12±4.08	13.61±4.49	<0.05
Primary end point: Death (%)	6.86	22.2	26.47	52.83	<0.001

Table 2: Comparison of baseline characteristics of the study population in the different ionized calcium groups

In our study, the mean APACHE II Score in normocalcemia group was 7.02±3.05. Mild,moderate and severe hypocalcemia groups had a mean APACHE II score of 14.28± 4.31,15.32± 4.83 and 21.68± 2.60 respectively which was statistically significant when compared with the normocalcemic group (p value <0.05)

The primary end point i.e death from all cause was seen in 22.2% of mild hypocalcemic group; 26.47% of moderate hypocalcemic group and 52.83% of severely hypocalcemic groups which was statistically significant when compared with the normocalcemic group (6.86%); p value <0.001

Also, the mean length of ICU stay (LOS) among the normocalcemia group was 6.58± 3.11 days and the mild, moderate and severe hypocalcemia group was 11.83 ± 4.09 days, 12.12 ± 4.08 days and 13.61± 4.49 days respectively which was statistically significant (Pvalue<0.05).

Characteristics	*Survivors*	*Non-survivors*	*Pvalue*
Age (years)	55.56 ± 15.99	54.25 ± 15.76	0.61
Mean APACHE II Score on admission	10.98 ± 6.48	18.73 ± 5.42	<0.05
Mean Ionized calcium on admission	1.09 ± 0.26	0.79 ± 0.23	<0.05

Table3: Characteristics between ICU survivors and Non-survivors

Though both the survivors and non- survivors had comparable age ,mean APACHE score (10.98± 6.48 vs 18.73± 5.42) was higher among non survivors while mean ionized calcium value (1.09± 0.26vs 0.79± 0.23 mmol/L) was lower amongst non survivors thereby showing an inverse relation between between admission APACHE II score and **Ca0**

IV. Discussion

Calcium is an essential electrolyte in human body and is associated with myriads of functions including blood clotting, muscle contraction, maintenance of cardiac rhythm, nerve conduction, glycogen metabolism and cell mitosis. 99% of calcium in human body is in the bones with the rest 1% in blood, muscles and other tissues. The human body has a well regulated calcium homeostasis where the calcium level is maintained within a narrow range. The regulation of calcium in human body is not regulated by absorption or excretion but rather by mobilisation of calcium from the bones by the action of osteoblasts and osteoclasts responding to hormonal signals. The intracellular calcium levels are also regulated but as the cells are bathed in extracellular fluid containing calcium, the entry of calcium into the cells is the limiting factor.

The initial reports of hypocalcemia being associated with critically ill patients were from 1970s and early 1980s.**[4]** Subsequentlty multiple studies have found hypocalcemia to be widely prevalent in critically ill patients admitted in hospital[5]. Multiple factors have been implicated as a cause of hypocalcemia in critically ill patients acting alone or in unison. These includes of proinflammatory cytokines, disordered action of PTH mainly end organ resistance and suppression of PTH, redistribution of extracellular and intracellular calcium ion and catecholamine release[6]

The impact of low calcium levels of critically ill patients can be by multiple mechanisms. The low calcium levels may cause hemodynamic changes affecting the mean arterial blood pressure, left ventricular stroke volume and cardiac output and can also precipitate seizures.

The present study showed that hypocalcemia on admission was a frequent finding in ICU patients.The prevalence of hypocalcemia in the study was 50.72% of which 25.60% had severe hypocalcemia. In a study conducted by Steele et al., hypocalcemia was a very common abnormality in patients upon admission to intensive care – 55% of patients had hypocalcemia which was close to the present study. Similar was also found in the study by Zhongheng Zhang et al (2014) [7] and Bairdetal (2009) [8].

The mean age of patient population in our study was 55.35± 15.85 years. There was no statistically significant difference between the mean age of normocalcemic (55.24±15.25years) and the hypocalcemic groups (55.07±16.53years); (p value =0.4). The non association of age with hypocalcemia was also the findings of studies by Tom Steele et al [9] and Kelly et al [10].

The 2nd version of the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score was introduced in 1985 and it included 12 parameters including body temperature, central arterial pressure, heart rate, respiratory rate, AaDO2 or PaO2, arterial pH, serum Na+ , serum K+ , creatinine, hematocrit, white blood cell count, and Glasgow Coma Scale (GCS), along with age with scores being given for all the variables generating a point score from 0 to 71. Measurement of Calcium on admission was not included in the calculation of APACHE II score. Subsequently, APACHE III and APACHE IV system were developed and introduced but those were more cumbersome and hence less often used. High APACHE II score during the first 24 hours of admission indicated a more severe disease with higher chances of adverse outcome.

The present study has shown that with the increase in the APACHE II score on admission, the ionized calcium levels was likely to be lower and this was found to be statistically significant.(p value <0.05). Also, there was statistically significant difference between the mean APACHE score of survivors vs nonsurvivors (10.98± 6.48 vs 18.73± 5.42); p value< 0.05. This finding of the present study is in accordance with studies conducted by Kelly et al [10],Zivin et al [11], Mobeen Iqbalet al[12], F.Afshinnia et al [13] and Constantine et al [14]

The study has also revealed that the patients belonging to the hypocalcemia groups had longer stay in the ICU. The mean length of stay of the severely hypocalcemic group was 13.61± 4.49 days and the difference was statistically significant (p value <0.05) when compared to the normocalcemic group. This finding of our study closely correlates with the findings of the studies conducted by Padhi R et al[10],Tom Steele et al [9], Chernow et al[15]

In the present study, 48 patients died with a mortality rate of 23.2%. When compared with the mortality of the normocalcemic patients, all the hypocalcemic groups (mild, moderate and severe) had increased mortality which had strong statistical significance - p value <0.05. This finding of the study is in accordance with the findings ofChernow et al[13],Padhi R et al [7], and Zhongheng Zhang et al[4].

The study population varies from study to study. The patients enrolled in the study were only from medical intensive care patients. In the study, among the different clinical conditions, highest incidence of hypocalcemia was seen among sepsis patients (91.43%) followed by acute encephalitis patients (76.92%),

cirrhosis patients (52.63%) and stroke (51.06%). Acute kidney injury was present in 33.33% of the hypocalcemic patients and respiratory diseases and cardiac illness was present in 31.58% and 28.57 % of the hypocalcemic patients respectively.

Hypocalcemia is a common finding in sepsis[16,17, 18,] .In the present study, among the different clinical conditions, sepsis patients had the highest mortality rates of 48.57%. The subgroup of severely hypocalcemic sepsis patients had the highest mortality rates of 52.94% when compared among the different calcium study groups with sepsis. Also, the mean APACHE score of the severely hypocalcemic group with sepsis was the highest i.e 22.65±2.23. Desai TK et al also in their study revealed that there was a strong association between sepsis and hypocalcemia.[19] In the study conducted by Ferreira et al [20] on severe sepsis and septic shock patients from June 2000 to June 2001, the incidence of hypocalcemia was 80% and that of severe hypocalcemia was 41.9% among the sepsis patients which was close to the study.

Hypocalcemia during sepsis is multifactorial in origin, resulting from acquired parathyroid gland in sufficiency, renal 1α-hydroxylase insufficiency, vitamin D deficiency, and acquired calcitriol resistance. In vitro studies have shown that the intracellular calcium metabolism is disturbed in sepsis patients, and that the changes in extra cellular calcium are probably secondary to the intracellular changes. Also parathyroid hormone secretion is inappropriate in septic patients. This may explain the strong association of sepsis and hypocalcemia.[20]

V. Conclusions from the study were as follows:

1. Hypocalcemia was a frequent occurrence in critically ill patients in medical ICU.
2. In a significant number of cases, the low serum ionized calcium levels on admission was inversely associated with high APACHE II scores of the patients. Thus, hypocalcemia on admission could be considered to be a marker of disease severity.
3. Estimation of serum calcium can be an easy prognostic indicator in critically ill patients especially in an intensive care set up.

The results of this study is to be viewed within limitation of the methods used.

1. The major limitation was smaller number of patients included in the study involving few diseases which necessitated ICU care.
2. The present study did not take into account few confounding factors like serum phosphate levels and parathyroid hormone levels due to constraints in resources and infrastructure.

Conflict of interest: Authors declare no conflict of interest. No financial aid was received for the study.

Acknowledgement: The authors express their gratitude to the other doctors working in the ICU, nursing staff and laboratory technicians for helping to carry out the research.

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Dr. Abhijit Swami MD, et. al. "Correlation of Admission Apache Ii Score and Hypocalcemia As A Severity Marker In Critically Ill Patients In Medical Intensive Care." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 22(3), 2023, pp. 27-32.