RESEARCH PAPER | Medical Science | Volume : 4 | Issue : 4 | Apr 2014 | ISSN - 2249-555X

Role of Calcium in Critically Ill Children-Incidence of Hypocalcemia in Pediatric Intensive Care Unit Set Up

KEYWORDS

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ABSTRACT *We have studied ionized serum calcium in a prospective cohort of 320 children (186 boys, 134 girls), admitted consecutively to a PICU of N.K.P.SALVE Institute and medical science Nagpur. and correlated it with the outcome.*

Venous blood was obtained for serum ionic calcium, at the time of admission . Hypocalcemia was present in 47.5 per cent of patients at admission and during hospital stay. which seems to be within range mentioned in the literature. Our cut off value of hypocalcemia was 1.12 mmol/l. It was found that hypocalcemia was more common in critically ill children with 114 (56.72%) cases as compared to non-critically ill children with 38 (31.9%) cases. Age and gender of the patient did not reveal any relationship with ionized calcium. Mortality was significantly higher in hypocalcaemic (17) compared with normocalcaemic (3) patients. We conclude that hypocalcemia is common in critically ill children admitted to a PICU and is associated with higher mortality

INTRODUCTION

Critical illnesses caused by any severe medical or surgical diseases may trigger an acute phase response which is associated with several metabolic derangements.[1] In the recent years, much attention has been focused on electrolyte imbalances observed in critically ill children. Electrolytes play a major role in most of the physiological processes from maintaining electrical properties across the membranes to the release of many hormones and muscle contraction. [2] At times, the disease process may come under control but the clinical condition might not improve due to underlying electrolyte disturbances going unnoticed. Hence, the role of routine electrolyte estimation in such critically ill children cannot be overemphasized. Calcium is a divalent action involved in many critical cellular processes. Total serum calcium exists in three forms:1) Ionized, normally 50% of the total; 2) Bound to plasma proteins such as albumin, usually 40% of the total; 3) Complexed to anions such as lactate and phosphate, usually 10% of the total. Initial ionized calcium (iCa), the physiologically active form of calcium found in the blood is regulated by homeostasis.[3] Calcium disturbances are the most commonly encountered electrolyte disturbances and have a very diverse clinical manifestations from apparently asymptomatic to severe life threatening situations. The normal range for total calcium is 8.8 – 10.8 mg/dl [4] and that of ionized calcium is 1.12 -1.23 mmol/L (4.8-4.92 mg/dL).[4] Hypocalcemia is defined as total serum Ca < 8.8 mg/dl [4] and ionized hypocalcemia as ionized Ca < 1.12 mg/dl.[4]

AIM

1) To study incidence of hypocalcemia in critically ill children admitted in Pediatric Intensive Care Unit.

OBJECTIVES

1) To correlate hypocalcemia with outcome, length of hospital stay.
2) To assess association of hypocalcemia with outcome in a heterogenous cohort of critically ill patients.

Study Design: Hospital based prospective Study.

Study Period: October 2011 – September 2013.

Study Setting: Pediatric Intensive Care Unit.

Study Population: All patients admitted in PICU.

Sampling Method: Non probability sampling.

Statistical Analysis: SPSS ver 11.0.

Inclusion Criteria: All patients admitted in PICU during the study period.

Exclusion Criteria: Any patients who falls under any of the following : -

1) Received calcium and vitamin D therapy IV at the time of or before admission.
2) Already received blood transfusion before sampling.
3) Received drugs such as furosemide (>2 mg/kg/day), methylprenisolone (>2 mg/kg/day) or phenytoin/phenobarbitone (at any dose).[5]
4) Known to have underlying chronic renal insufficiency.
5) Are already on treatment for malignancy.
6) Parents who are unwilling for the investigation.
7) Patients with hypercalcemia.

MATERIALS AND METHODS

The hospital based prospective study was carried out in a 10 bedded PICU with approximate admission of 190 annually. The patients were between the ages 1 month to 18 years. 2 ml of free flow of venous blood was taken without applying a tourniquet in a plain bulb and centrifuged to collect for estimation of ionic calcium by a COBAS B 121 ion selective electrode machine. Blood samples for ionic calcium was collected within 48 hours or at any point during the hospital stay in PICU and if the patient had low values of ionic calcium were included in my study.

Normal Ionic Calcium was Taken As 1.12 – 1.23 mmol/L.

Ionized Hypocalcemia was Taken As < 1.12 mmol/L.

Demographic data, primary diagnosis, primary reason for admission, any need for respiratory support or cardiac support, length of hospital stay and outcome of the patients (Death, Discharge) was recorded. Written and informed consent was obtained from the parents.

Patients who satisfied the inclusion criteria were then categorized into following groups:[6]

CATEGORY A: Critically ill children were defined as those

Volume : 4 | Issue : 4 | Apr 2014 | ISSN - 2249-555X

who were admitted in PICU and stayed for more than 48 hours or died in the 1st 48 hours of admission.

CATEGORY B: Non critically ill children were defined as those children who were admitted in PICU and stayed less than 48 hours then transferred to the ward or discharged.

OBSERVATIONS AND RESULTS

A total of 432 cases were admitted during the study period out of which 81 cases did not meet the inclusion criteria, 31 cases did not consent to participate in the study; thereby leaving 320 cases for the study.

The study included 2 groups of children admitted in Pediatric Intensive Care Unit, critically ill (Category A) and non-critically children (Category B) and frequency of hypocalcemia and its effect on disease course was then compared in the two groups.

In a study sample of 320, there were 152 cases of hypocalcemia, giving an **incidence of 47.5%**. Out of 320 cases studied, 201(62.8%) cases were included in category A and 119 (37.2%) cases were included in category B.

Table 1 : Distribution of hypocalcemia subjects according to age (Category A)

Age category [7]	No. of subjects (%)		Total (%)
	Hypocalcemic	Normocalcemic	
Infant (< 2 yrs)	27 (45.00)	33 (55.00)	60 (29.8)
Young child (2-6 yrs)	39 (79.59)	10 (20.41)	49 (24.4)
Child (6-12 years)	28 (49.12)	29 (50.88)	57 (28.4)
Adolescent (12-18 yrs)	20 (57.14)	15 (42.86)	35 (17.4)
Total	114 (56.72)	87 (43.28)	201

***P*-value: 0.0017 as per** *Chi-square test*

Table 1 provides the distribution of subjects according to age and hypocalcemia. Maximum, i.e. 60 (29.8%) subjects were observed in the infant age group. Amongst the infants, 27 (45.00%) cases were hypocalcemic, while 33 (55.00%) were normocalcemic. In the adolescent i.e. 12-18 yrs age group, out of 35 (17.4%) subjects, 20 (57.14%) cases were hypocalcemic, while 15 (42.86%) were normocalcemic.

Table 2:Distribution of hypocalcemia patients as per age and gender (Category A)

Age category	No. of hypocalcemia cases (%)		Total (%)
	Male	Female	
Infant (< 2 yrs)	20 (74.07)	7 (25.93)	27 (23.68)
Young child (2-6 yrs)	27 (69.23)	12 (30.77)	39 (34.21)
Child (6-12 years)	18 (64.29)	10 (35.71)	28 (24.56)
Adolescent (12-18 yrs)	10 (50.00)	10 (50.00)	20 (17.55)
Total	75 (65.79)	39 (34.21)	114

***P-value: 0.3515 as per Chi-square test**

The distribution of hypocalcemia patients according to age and gender has been shown in Table 2. The number of hypocalcemic males was 75 (65.79%), which was higher than that of females i.e. 39 (34.21%).In the age group of 2-6 yrs, 27 (69.23%) patients were males, while 12 (30.77%) were females. There was statistically insignificant association between age and gender in this diseased group with *P*-value 0.3515 ($P > 0.05$) as per *Chi-square test*.

In hypocalcemic group, 41 patients were admitted for neurological causes (CNS), followed by 19 admitted for respiratory disorders. The respective break ups are given in the table. Overall, in category A, maximum number of cases [67 (33.33%)] admitted in our PICU were due to neurological causes out of which 61.19% were hypocalcemic and 38.81 % were normocalcemic. Viral encephalitis comprised maximum cases (30), out of which 19 (63.33%) had hypocalcemia. This was followed by seizure disorder which had 8 (57%) cases of hypocalcemia. Respiratory disorders were the second most common reason for admission to PICU [37 (18.40%)]. Out of these cases, Pneumonia occurred in 17 (43.24%) of cases. There were 14 (12.33%) cases admitted due to infectious cause and had hypocalcemia, out of these, 8 cases were of dengue. There were 3 (18.75%) cases of septicaemia grouped under infectious cause, but septicaemia was also seen as a complication in 2 cases of diseases due to GIT illnesses and one case of diabetic ketoacidosis. Out of 6 cases of septicaemia 5 (83%) hypocalcemia. Other common illnesses for which the patients were admitted was due to congenital heart disease, pancreatitis, acute renal failure, chronic liver disease and hematological causes. Cases of snake bite (1), diabetes ketoacidosis (3) and also showed hypocalcemia.

The association between of hypocalcemia and cardio-respiratory support was statistically significant with *P*-value 0.0035 ($P < 0.05$). The association between hypocalcemia and occurrences of deaths was statistically significant with *P*-value 0.0014 ($P < 0.05$) as obtained through *chi-square test*. This table shows that patient with hypocalcemia spent a longer time in ICU, and have longer mechanical ventilation days, require vasopressor support and have higher mortality rate.

Results (Category B)

Out of 119 cases of category B, 38 (31.9%) cases were hypocalcemic and 81 (68.1%) cases were normocalcemic.

In category B there were 38 (31.9%) hypocalcemic cases and 81 (68.1%) normocalcemic cases in this group. Out of 37 infants, 13 (35.13%) were hypocalcemic, while 24 (64.87%) cases were normocalcemic.

In group B it shows that there were 18 (47.37%) males and 20 (52.63%) females. In the infant category, out of 13 patients, 5 (38.46%) were males and 8 (61.54%) were females.

In group B hypocalcemia, maximum i.e. 10 (33.33%) patients were admitted for neurological causes (CNS), which had more number of normocalcemic patients. The primary diagnosis at the time of admission maximally included febrile convulsions an seizure disorders. Next common cause of admission was due to respiratory problems which again had more number of normocalcemic patients and included cases of Pneumonia or Asthmatic Bronchitis.

Other common illnesses for which the patient was admitted included congenital heart disease, acute gastroenteritis, hematological diseases, Dengue fever and cholestatic jaundices.

In order to determine the relation between occurrence of death and calcium status i.e. normocalcemia and hypocalcaemia as explanatory variable in presence of covariates age and sex, logistic regression analysis was performed. Normocalcemic was considered as reference level. The goodness of fit of model was evaluated using *Hosmer-Lemeshow test*, which resulted into a *P*-value of 0.888 indicating a good fit of the data. Further, the classification accuracy of the model was 93.8%.

DISCUSSION

Electrolyte disturbances are a common accompaniment of many disease states and hypocalcemia is often found in critically ill patients, adults as well as children. This association has not been extensively studied in terms of cause as well as

Volume : 4 | Issue : 4 | Apr 2014 | ISSN - 2249-555X

effects on the disease course. The present study was mainly directed towards, establishing this association and to determine if it played a role in the disease course of a critically ill child. Hypocalcemia has a prevalence of 18% in all patients in hospital and 85% in icu.[8] hypocalcemia has been reported in 12–90 per cent of critically ill adults[9,10,11,12] and children.[13,14,15]

Incidence
Our data also suggested that hypocalcemia is common during in study sample of 320 cases in PICU, there were 152 cases of hypocalcemia, giving an incidence of 47.5 %, which seems to be within range mentioned in the literature. Our cut off value of hypocalcemia was 1.12 mmol/l. It was found that hypocalcemia was more common in critically ill children with 114 (56.72 %) cases as compared to non-critically ill children with 38 (31.9 %) cases. The difference in the proportion of hypocalcemic cases in two groups was statistically significant with P-value < 0.0001 as per z-test of proportion.

Our incidence finding was near to a study conducted by Mobeen Iqbal in 2008 in Saudi intensive care unit set up who noticed hypocalcemia, a common finding in critically ill patients as high as 54%.[16] And also to a study conducted by Steele, who also found hypocalcemia a very common abnormality in patients upon admission to intensive care and reported a prevalence of 55%,they chose an ionized calcium concentration of 1.1 mmol/L as cutoff.[17]Gautheir studied 45 patients and found 14% patients to be hypocalcaemic.[25] In a study performed by Desai Tk et all (1988), total and serum ionized calcium levels evaluated upon admission of all patients, found to have decreased levels of both in 70% of patients.[19] Broner found 17% of hypocalcemia in the patients.[14] Zaloga summarized the incidence of total hypocalcemia at 70-90% and of ionized hypocalcemia at 15-50% in critically ill adults.[9]. Zivin found 88 % of Hypocalcemia in hospitalized patients.[10]

In our study, we considered only ionic calcium because this represents the physiologically active fraction; accounting for 50% of total serum calcium.[3,21] Moreover, this measure is not influenced by other alterations that may be present in acutely ill patients, such as disturbances in acid-base balance or hypoproteinemia.

None of the patients had symptoms attributable to hypocalcemia. Such features may be difficult to elicit in critically ill patients, since sedation and paralysis may eliminate signs of neuronal irritability, and intubated patients may be unable to express their symptoms. 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.

Age and Sex wise distribution
Out of the total 320 cases, 186 were Males (93 hypocalcemic and 93 normocalcemic) and 134 Females (59 hypocalcemic and 75 normocalcemic).

The mean age for males was (5.34 ± 4.74) and that for females was 5.26 ± 4.81 mean value of ionic calcium for males was 1.05 ± 0.21 and for females was 1.10 ± 0.17. Age and gender of the patient did not reveal any relationship with ionized calcium. This was similar to the study by Singhi and Singhi who also did not find any relationship of age and gender with calcium status.[22]

Length of hOspital stay
In our study in critically ill patients, mean duration of hospital stay for hypocalcemic was 6.61 ± 4.54 which was significantly higher than that of normocalcemic which was 4.80 ± 3.65 in the same category. This was consistent with the finding by Singhi et al, who also found longer duration of hospital stay of hypocalcaemic patients.[22] Pardhi et al, also found that the ionized hypocalcaemic patients spent a longer time in ICU.[23] Broner CW et al, also found that hypocalcemia was associated to longer ICU stay.[14] Also, in a study by Steele et al, patients with low ionized calcium had a longer stay on the ICU, and this finding was most prominent in severely hypocalcaemic patients.[17]

Systemwise distribution of hypocalcemia
In critically ill category with respect of the primary diagnosis, almost 60% cases admitted were for either neurologic or respiratory problems. In cases with CNS problems 61% cases and 51% cases with problems involving respiratory system had hypocalcemia. This finding was consistent with that of study by singhi et al,[22] and that by Maysa et al,[6] who also found more number of neurologic and respiratory cases as primary diagnosis upon admission. In our study we had 6 cases of septicaemia out of which 83 % had hypocalcemia. Singhi found hypocalcemia more common in patients with sepsis and shock.[22] Other common illnesses for which the patient were admitted was due to congenital heart disease, pancreatitis, acute renal failure, chronic liver disease and hematological causes. In a study by Pardhi, risk factors for hypocalcemia included severe sepsis, trauma, renal failure patients and those who had undergone emergency surgery.[23] Gallardo found more number of mortality in septic patients.[24]

Cardio - respiratory support
In hypocalcaemic group, 32(28.07 %) patients required cardio-respiratory support, while in normocalcemic group, only 9 (10.34 %) patient's required cardio-respiratory support. There were significantly higher proportions of hypocalcaemic patients requiring the cardio-respiratory support as compared to normocalcemic patients.

Cardenas et al in 1989 mentioned that hypocalcaemics required the administration of vasopressor agents more often than their normocalcemic counterparts.[13] Pardhi et al also found that patients with low serum ionized calcium values had longer mechanical ventilation days.[23]

Mortality
In present study we found more number of mortality in the hypocalcemic patients as compared to the normocalcemic patients of the same category. Amongst the 17 death that occurred, and almost 35% deaths was due to sepsis, 47% deaths occurred due to CNS disorders, and 11% death were due to respiratory disorders. The cause of the hypocalcemia is uncertain. Several mechanisms have been proposed to explain the underlying causes of hypocalcemia in critically ill patients. Although, we did not examine the causes of hypocalcemia in critically ill, it has been attributed to elevated calcitonin,[15] impaired parathyroid hormone secretion or action, impaired vitamin D synthesis or action, or circulating chelators.[9,12,19] Recent studies indicate that hypocalcemia in sepsis is related to inflammatory response, is not a result of increased urinary excretion of calcium or attenuated bone resorption,[27] and that a calcitonin precursor has a likely role.[15,25] .

CONCLUSION
Hypocalcemia appears to be common among PICU patients with an incidence of 47.5%.

The need for cardio-respiratory support amongst critically ill PICU patients was found to be increased in presence of hypocalcemia. Presence of hypocalcemia probably represents a sign of more severe disease.

Children who were critically ill and also had hypocalcemia had a significantly poorer outcome in terms of mortality or longer length of hospital stay . However, subsequent prospective interventional trials are required to establish whether correction of calcium has an impact on critical illness disease course and outcome.

Volume : 4 | Issue : 4 | Apr 2014 | ISSN - 2249-555X

LIMITATIONS

We studied calcium status in only acute illness, there are also other conditions attributing to hypocalcemia like any drug intake like diuretics, corticosteroids, anticonvulsants, recent blood transfusion etc an any other chronic disease causing hypocalcemia, which would have increased the overall incidence of hypocalcemia.

We did not work upon the causes of hypocalcemia which needed expensive investigations like parathormone, calcitonin, vitamin D levels, facilities for which are not available at our institute.

As the present study was conducted in a tertiary referral unit where children may be referred from various parts of the state in a more debilitated condition, high prevalence of hypocalcemia in one study group can be explained. This may not represent the true incidence seen in general population.

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