ISSN- O: 2458 - 868X, ISSN –P: 2458 - 8687

International Journal of Medical Science and Innovative Research (IJMSIR)

IJMSIR : A Medical Publication Hub

Available Online at: www.ijmsir.com

Volume – 2, Issue –6, November – December - 2017, Page No. : 230 - 236

Calcium Disturbances in Critically Ill Children Admitted To Pediatric Intensive Care

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Conflicts of Interest: Nil.

Abstract

Background: The aim of the study was to determine the incidence and length of ICU stay in children with calcium disturbances admitted to pediatric intensive care unit (PICU)

Methodology: Descriptive prospective study during one year in children aged 1 month to 12 years. A total of 101 critically ill children were included in the study

Results: The incidence of hypocalcemia (Serum calcium < 8.8 mg/dL) was 41.6% (n=42) and hypercalcemia (Serum calcium >10.8 mg/dL) was 3% (n=3) respectively. 01 month - 4yrs age (41.2%) group of our study population, emerged as a susceptible age group to calcium disturbances, with mean age 4.36 ± 4.10yrs. In hypocalcemia 47.6% and hypercalcemia 100% were grouped under the age 01 month – 4 yrs. Majority of the patients were boys, accounting for 60.4% of the study participants. Hypocalcemia was seen in 61.9% boys and hypercalcemia in 100% boys. Hypocalcemia was observed in all etiological categories with CNS (40.5%), respiratory (14.3%), GI disorders (11.9%) responsible for majority of cases. Hypercalcemia was noted in CNS (66.7%) and CVS (33.3%) disorders only. Mean length of stay in hypocalcemia and hypercalcemia were 7.77 ± 6.377 days and 4.67± 2.082 days respectively and was more compared to normal calcium levels. Of the 11 children who required inotropic support during the course of their ICU stay, 54.5 % (6) were hypocalcemic and 18.8 % had combined electrolyte disturbances. The requirement of ventilation is higher in hypocalcemia compared to normal calcium levels (14.5% vs. 5%). The mortality rate was significantly higher in the hypocalcemic group v/s the normocalcemic patients (9.5% vs. 5.4%) and was found to be 1.7 times higher in hypocalcemic patients.

Conclusion: Disturbances in the serum calcium levels during the ICU stay in our study children predicted an increased length of hospital stay and low serum levels were associated with increased inotropic use and mechanical ventilation, indicating a stormy PICU course, with dismal patient outcome in terms of survival, emerging as an independent risk factor for mortality.

Keywords: Critically ill children, Hypocalcemia, ICU stay, Mortality

Background: Calcium, which exists in the body as a divalent cation (Ca^{2+}), plays a critical role in regulating diverse physiologic processes such as neuromuscular signalling, cardiac contractility, hormone secretion, blood coagulation, secretory activity, cell death, cell differentiation, immune response and enzyme activation. Approximately 99% of the total body calcium resides in

the skeleton, whereas the remaining 1% is found in the soft tissues and extracellular spaces. Approximately 40% of plasma calcium is bound to protein, principally albumin, 10% Ca^{2+} is in complex with various anions and 50% as free Ca^{2+} ions (ionized calcium, or iCa). iCa is the physiologically important fraction of plasma calcium and its concentration is tightly regulated by parathyroid hormone (PTH),1,25 dihydroxyvitamin D [1,25(OH)2D], Calcitonin and iCa itself acting on three major organs: the kidneys, intestinal tract and bone. [1]. Published normal values for total serum calcium range from 8.8-10.8 mg/dL [2, 3].

Hypocalcemia is one of the most frequent electrolyte abnormalities encountered in the ICU. Low total concentrations of calcium have been reported to be affecting as many as 90% of critically ill patients [4] and the prevalence of hypocalcemia measured as ionized calcium and total serum calcium is estimated to be 17-70% [5-8] and 22-70% [5,6,9,10]. Hypocalcemia is associated with increased mortality in patients cared in the ICU [10, 11]. The hypocalcemia in critically ill patients is the consequence of suppression of PTH secretion by cytokines, increase calcium binding to albumin, PTH deficiency, impaired renal hydroxylation of vitamin D. Sepsis related hypocalcemia is due to bacteremia and effect of inflammatory mediators on PTH secretion and action [12, 13].

Hypercalcemia results from the failure of renal calcium excretion to compensate increased influx of calcium into the circulation from the intestine, kidneys and skeleton. Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases. Data in children with cancer indicates a lower frequency of hypercalcemia (about 0.5-1%) [14].Symptoms of hypercalcemia are non specific and most symptoms and signs are related to underlying disease. The present study was undertaken to study the calcium disturbances in critically ill children seeking emergency care in the PICU as the various studies quoted above pertain to adult population and there is paucity of data in pediatric population.

Aims & Objectives

To evaluate the incidence, length of ICU stay and outcome of calcium disturbances in critically ill children in a tertiary care centre.

Methodology

This prospective study was conducted over a period of one year and included critically ill children aged 1 month to 12 years admitted to a paediatric intensive care. Ethical clearance was obtained from Institutional Ethical Committee. Informed consent was obtained from the parents of all the children enrolled in the study.

Inclusion Criteria

Children of age group 1 month to 12 years, admitted in the PICU with severe clinical condition requiring intensive care, satisfying the criteria based on the Consensus Guidelines for PICUs in India, Indian Society of Critical Care Medicine (Paediatric Section) and Indian Academy of Paediatrics (Intensive Care Chapter).[15]

Exclusion Criteria

Include

i). PICU stay of less than 24 hours.

ii). Infants < 1 month old.

iii). Children transferred in from other service/civil hospital.

iv). Children with already diagnosed electrolyte disturbances, e.g. Bartter syndrome.

At admission, detailed history was taken and systemic examination was recorded. Venous blood samples were obtained and serum calcium was estimated by using Combi line Ion-Selective Electrode (ISE). An Ion-

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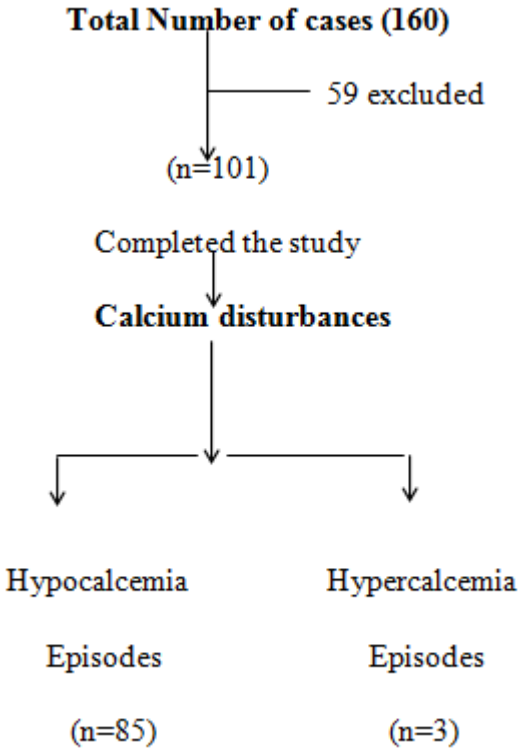
Selective Electrode (ISE), also known as a specific ion electrode (SIE), is a transducer (or sensor) that converts the activity of a specific ion dissolved in a solution into an electrical potential, which can be measured by a voltmeter or pH meter.

If a calcium abnormality was found during ICU stay complete blood count, urea, creatinine, phosphorus, albumin and alkaline phosphatase levels were done. Vit-D and PTH levels were done based on calculated calcium levels. In hypercalcemia Phosphorus, Vit-D and PTH levels were done. . If required special investigations USG, X-ray, CT, MRI and other relevant investigations as required for diagnosis and treatment of patient were done. Neuroimaging was done by Computed Tomography or Magnetic Resonance Imaging using 1.5 Tesla Magnetom Avento magnetic resonance imaging machine in the hospital itself. In case calcium abnormality was noted multiple times during ICU stay, numbers of episodes of electrolyte disturbances were documented. For analysis outcome and other statistical calculations, electrolyte abnormality at an extreme range (e.g. lowest recording during ICU stay) was taken into consideration. Hypocalcemia in our study was defined as serum calcium < 8.8 mg/dL and hypercalcemia as serum calcium >10.8 mg/dL. Data was analysed using Statistical Package for Social Sciences version 19.0. The values were represented in Number (n) and Mean +/- SD. The following statistical values were employed: Mean, Standard deviation, Chi-square tests (x2) and level of significance (p)

Results

A total of 160 cases were admitted during the study period, out of which 59 cases did not meet the inclusion criteria, thereby leaving 101 cases for the study.

Consort Flow Chart Showing the Establishment of Electrolyte Disturbances



A. Sex and Age Distribution

Of the 101 children studied, 61 (60.4%) were boys and 40 (39.6%) girls. Majority (56.4%) were in the age group of 1 month - 4 years, 23.8% of the children were between 5 – 8 years of age and the remaining 19.8% were between 9 – 12 years of age. Mean age of the study population was 4.36 ± 4.10 years. Boys out number girls in both hypo and hypercalcemia. Distribution of age and sex were represented in Table 1.

B. Incidence

The incidence of hypocalcemia (Serum calcium < 8.8 mg/dL) was established at 41.6% (n=42), hypercalcemia was 3% (n=3) and normocalcemia 55.4% (n=56). Episodes of electrolyte disturbances include hypocalcemia 85 and hypercalcemia 3. Incidence of calcium disturbances were represented in Table 1.

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C. Spectrum of Illness

Hypocalcemia was observed in all etiological categories with CNS, respiratory, GI disorders responsible for majority of cases. Hypercalcemia was noted in CNS and CVS disorders only. Table 2 represents the spectrum of illness

D. Length of the Hospital Stay

Mean length of stay in hypocalcemia and hypercalcemia were 7.77 ± 6.377 days and 4.67± 2.082 days respectively. This implies increased length of stay in calcium disturbances compared to normocalcemia (4.47+-2.91 days) which was statistically significant($p<0.05$) as shown in Table 3.

E. Blood transfusion

Blood transfusion was received in 31% of hypocalcemia children and diuretic use was noted in 47.6% and 33.3% of hypo and hypercalcemic children respectively. Both blood transfusion and diuretic use had a statistical significant difference ($p<0.05$)

F. Inotrope and Ventilation

11 children in our study population required inotropic support. 6 children with hypocalcemia (54.5%) required inotropic support. None of hypercalcemic children required inotropic support. 9 children required mechanical ventilation in our study. 3 children were noted to have combined electrolyte disturbances. The requirement of ventilation is higher in hypocalcemia compared to normal calcium levels (14.5% vs. 5%). None of hypercalcemic children required ventilation. Inotrope use, ventilation and mortality are shown in Table 4.

G. Mortality

7 children in our study population expired. The mortality rate was significantly higher in the hypocalcemic group v/s the normocalcemic patients (9.5% v/s 5.4%) and was found to be 1.7 times higher in hypocalcemic patients.

Discussion

Our study suggested that hypocalcemia is common in PICU at an incidence of 42%, this seems to be within range mentioned in the literature. Our incidence finding was near to a study conducted by Cardenas *et al* [5], Neha *et al* [6] and Saeedeh *et al* [7]. Contrary to our results Broner *et al* [16] and Singhi *et al* [9] noted lower incidence of hypocalcemia which may be due to different cut off value used for defining hypocalcemia. The incidence of hypercalcemia is 3% in our study. This is in consistent with studies by Christenson *et al* [11], Palmer *et al* [17] and Shek *et al* [18] who reported the incidence of hypercalcemia ranging from 1% - 3.5%, similar to my observations. However studies by these authors recorded hypercalcemia in general ward patients and malignancy related hypercalcemia.

Hypocalcemia in our study was noted in 62% of boys with boys to girls' ratio of 1.6: 1. Neha *et al* [6] and Steele *et al* [19] in consistent with our results reported higher incidence of hypocalcemia in boys with boys to girls' ratio of 1.8:1 and 1.2:1 respectively. In our study all the 3 cases of hypercalcemia were noted in boys. No similar observations were noted in literature search.

The mean age of hypocalcemic children in our study was 5.12 ± 4.54 years. Majority (47.6%) were of 01month to 4 yrs, 23.8% were between 5- 8 yrs and 28.6% were between 9- 12 yrs respectively. Consistent with our study Maysa *et al* [4] observed mean age of hypocalcemic children was 3.16 ± 0.2 yrs. Neha *et al* [6] in their study distributed the hypocalcemic children according to age as 25% were <2 yrs, 34.2% were between 2-6 yrs, 24.5% were between 6-12 yrs and 17.5% were between 12-18 yrs respectively. Mean age of hypercalcemic children was 1.75 ± 1.52 yrs with all the three children in age group of 01 month - 4 yrs.

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The diagnostic categories for hypocalcemia in our study included all the etiologies, with majority of cases included were CNS disorders (40.5%), respiratory (14.3%) and GI disorders (11.9%). Less common causes were sepsis (7.1%), renal (7.1%), CVS (7.1%), miscellaneous (7.1%) and haematology (4.8%). Saeedeh *et al* [7] reported the diagnostic categories of hypocalcemia as CNS (25.5%), infections (22.4%), respiratory (21.3%), poisonings (9.9%), CVS (8.5%), GIT (5.8%) and metabolic disorders (4.8%) similar to our results. Neha *et al* [6] in their study, observed the causes of hypocalcemia were due to neurological (35.9%), viral encephalitis (16.6%), seizure disorder (7%), pneumonia (14.9%), infections (12.2%), sepsis (5.2%), snake bite (1%) and diabetic ketoacidosis (2.6%). The observations regarding CNS, sepsis and respiratory disorders were similar. 3 cases of hypercalcemia in our study were grouped under CNS (66.7%) and CVS (33.3%). Saeedeh *et al* [7] reported no case of hypercalcemia. The studies reported hypercalcemia was related to malignancy disorders. Reasons for discrepancy could not be ascertained.

In our study in critically ill patients, mean duration of hospital stay for hypocalcemic was 7.77 ± 6.37 days, which was significantly higher than that of normocalcemic, which was 4.47 ± 2.91 days. This was consistent with the finding by Singhi *et al* [9], who also found longer duration of hospital stay of hypocalcemic patients. Broner CW *et al* [16], also found that hypocalcemia was associated to longer ICU stay.

In hypocalcemic group, 6 (14.3 %) patients required inotrope support, while in normocalcemic group, only 5 (8.9 %) patient's required cardio-respiratory support. There were significantly higher proportions of hypocalcemic patients requiring the inotropic support as compared to normocalcemic patients. Cardenas *et al* [5] mentioned that hypocalcaemics required the administration of vasopressor agents more often than their normocalcemic counterparts. Neha *et al* [6] also found that patients with low serum ionized calcium values had required vasopressor support. In contrast to the above studies, Saeedeh *et al* [7] found no significant difference in inotrope use in hypocalcemic and normocalcemic children.

In our study, 7.1% of hypocalcemic children were ventilated. Of the 9 ventilated children in our study, 33.3% were hypocalcemic, implying a higher ventilation rate with hypocalcemia compared to normocalcemia (16.7% vs 5.4%). Neha *et al* [6] also found that patients with low serum ionized calcium values had increased ventilatory requirement akin to our observation. None of the hypercalcemic children were ventilated.

Mortality in hypocalcemia (11.6%) was 2.12 times higher than normocalcemic (5.45%) children. Our results were consistent with Cardenas Rivero *et al* [5] who reported 31% deaths with ionized hypocalcemia versus 2.5% with normocalcemia. Saeedeh H *et al* [7] noted mortality in hypocalcemia in 45% children compared to 24.8% in normocalcemia. Singhi *et al* [9] reported, mortality was significantly higher in hypocalcemic (28.3 per cent) compared with normocalcemic (7.5 per cent) patients ($p < 0.05$).

All the three children with hypercalcemia recovered in our study. These results were contradiction with Zhongheng Zhang *et al* [20] who observed increased mortality in patients with hypercalcemia. Incidence of hypercalcemia was very low and the limited sample size may significantly compromise the statistical power. However, based on current evidence, the clinical significance of hypercalcemia cannot be determined and further investigations are needed.

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Table 1: Demographic Characteristics and Incidence of Calcium disturbances

Calcium abnormality	Incidence No. (%)	Age Distribution No. (%)			Sex Distribution No. (%)	
		1 M-4 Y	5-8 Y	9-12 Y	Boys	Girls
Hypocalcemia(n=42)	42(41.6 %)	20(47. 6)	10(23. 8)	12(28. 6)	26(61. 9)	16(38. 1)
Hypercalcemia(n=3)	3(3%)	3(100)	0	0	3(100)	0(0)

Table 2: Spectrum of illness in calcium disturbances

Diagnosis	Normocalcemia (n=56)		Hypocalcemia (n=42)		Hypercalcemia (n=3)		Total (n=101)	
	No	%	No	%	No	%	No	%
Respiratory disorders	18	32.1	6	14.3	0	0	24	23.8
Sepsis	4	7.1	3	7.1	0	0	7	6.9
GI disorders	11	19.6	5	11.9	0	0	16	15.8
Renal disease	3	5.4	3	7.1	0	0	6	5.9
CVS	1	1.8	3	7.1	1	33.3	5	5
CNS	15	26.8	17	40.5	2	66.7	34	33.7
Hematology	2	3.6	3	7.1	0	0	5	5
Miscellaneous	2	3.6	2	4.8	0	0	4	4
Total	56	100	42	100	3	100	101	100
P	0.337							

Table 3: Length of stay in Calcium disturbances

Calcium abnormality	1-5 days		6-10 days		>10 days		Statistical significance	
	No.	%	N	%	No	%	x^2	P
Hypocalcemia(n=42)	26	61.9	6	14.3	10	23.8	**11.13**	**0.025**
Hypercalcemia(n=3)	2	66.7	1	33.3	0	0		

Table 4: Ionotropes, Mechanical ventilation and Mortality in Calcium disturbances

Calcium Abnormality	Inotrope Usage (n=11)		Mechanical Ventilation (n=9)		Mortality (n=7)	
	No.	%	No.	%	No.	%
Hypocalcemia(n=42)	6	54.5%	6	66.6%	4	57.1%
Hypercalcemia(n=3)	0	0	0	0	0	0
Normocalcemia(n=56)	5	45.4%	3	33.3%	3	42.9%

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