Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

Incidence of Hypocalcemia in Patients at Surgical Intensive Care Unit

Zeinab Ibrahim Ahmed El hossary, Sahar Mohammed Saad Eldin, Heba Helmy Matar, Ibrahim Abdel-Halim Askar

Anesthesia and Surgical Intensive Care Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Ibrahim A. Askar, Email: Ebrahimasker96@gmail.com

ABSTRACT

Background: The incidence of hypocalcemia in critically ill patients varies widely depending on the different underlying diseases and comorbidity. The aim of the study is early prediction of cases of hypocalcemia for better management and to improve morbidity and mortality in patients of surgical intensive care unit of Zagazig University Hospitals.

Patients and methods: A prospective cohort study included 310 patients and was carried out in the surgical intensive care unit of Zagazig University Hospitals over a period of six month. Total serum calcium concentration was measured colorimetrically, whereas the serum ionized calcium concentration was measured using an ion-selective electrode method.

Results: The present study included 310 patients who were admitted to ICUand their calcium level was measured. The mean age of the studied cases was 50.58±14.31 years ranging from 22 to 80 years, 51% were females and mean duration of ICU admission was 7.12±2.45 days ranging from 3 to 14 days. About 41% of the cases developed hypocalcemia on the third day of follow up and 59% of the studied cases developed hypocalcemia on the 5th day of follow up. The current demonstrate that 40% of the studied cases were admitted to ICU due to sepsis and septic shock, 16% polytrauma , 10% respiratory failure, 10% post-operative monitoring , 6% with ICH , 6% with uncontrolled HTN, 4%with ischemic stroke, 2% pancreatitis , 2% dehydration & electrolyte imbalance , 2% DKA and one case due to organophosphorus poisoning and 1% rhabdomyolysis. The mean GCS was 11.79±2.16 ranging from 6 to 15 ,mean APACHE2 score was44.25±18.7 ranging from 2 to 50, mean creatinine 1.64±1.36 ranging from 0.5 to 6.3 , mean Urea 43.22±41.6 ranging from 12 to 170 , mean albumin 3.43±.64 ranging from 2 to 5 , mean Ph 3.46±.5 ranging from 2.6 to 4.5 and mean Mg was 1.88±.29ranging from 1.2 to 2.6. The present study showed 82% of the studied cases were treated with heparin, 79% with PPI , 21% diuretics and 18% aminoglycosides.

Conclusion: Hypocalcemia is a frequent complication that could be encountered in the critically ill patients.Based on our findings incidence rate of hypocalcemia at 5th day of ICU admission is (59%) which is larger than that at 3rdday (41%) .

Keywords: Hypocalcemia ; Ill patients ; ICU

INTRODUCTION

Hypocalcemia defined as total serum calcium level lower than 8.5 mg/dl or an ionized serum calcium level lower than 4.7 mg/dl is relatively common metabolic abnormality observed in hospitalized patients. Although it is associated with certain pharmacological agents such as biphosphonates and cisplatins, hypocalcemia may occasionally develop in the course of treatment with some drugs including antiepileptics, aminoglycosides and proton pump inhibitors **(1)**.

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 **(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)**. About 99% of the calcium in the body is stored in bone mainly as hydroxyapatite crystals. About 1% of calcium is freely exchangable with the extracellular fluid compartment (ECF) and therefore is available to buffering changes in calcium balance. Total serum calcium concentrations in healthy people range from 8.8 to 10.4 mg/dl or 2.20-2.60 mmol/l. About 40% of the total blood calcium is bound

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

to plasma proteins. The remaining 60% includes ionized calcium and calcium complexed with phosphate and citrate. Ionized calcium is the physiologically active form which acts as an intracellular second messenger. It is involved in skeletal muscle contraction, excitation-contraction coupling in cardiac and smooth muscle and activation of protein kinases and phosphorylation leading to the formation of other second messengers as cAMP and inositol 1,4,5-triphosphate mediating the cellular response to numerous hormones including epinephrine, glucagon, secretin and cholecystokinin **(4)**. Electrolyte disturbances like hypocalcemia affect many fundamental physiologic regulatory mechanisms. Calcium metabolism abnormalities can lead to serious cardiovascular complications and organ dysfunctions **(5)**. The aim of the study is early prediction of cases of hypocalcemia for better management and to improve morbidity and mortality in patients of surgical intensive care unit of Zagazig University Hospitals.

PATIENTS AND METHODS

A prospective cohort study included 310 patients and was carried out in the surgical intensive care unit of Zagazig University Hospitals over a period of six month from July to December 2019. Approval was obtained from Institutional Review Board at Zagazig university hospitals. The study procedures were free from any harmful effects on the participants as well as the service provided.

Inclusion criteria:

All patients above 18 years old admitted to surgical intensive care unit of Zagazig University Hospitals with normal calcium level over period of 6 months

Exclusion criteria:

Patients with hypocalcemia on admission.Previous hospital admission within 2weeks before presentation. Supplementation vitamin D therapy at time of admission.Current treatment for malignancy. Preexisting or known parathyroid disease.

Operative Assessement:

All patients were from each patient the following data was collected upon admission: age, gender (both), other co morbidities, calcium level (total and ionized) from day of admission , 3rd day and 5th day if the patient still admitted to ICU, cause of admission to ICU, hospitals diagnosis, ICU stay in days and date of discharge, APACHE II score at time of ICU admission. Routine lab including (magnesium, phosphorus, albumin, urea and creatinine at 3rd day of admission). Medications example :(diuretics, heparin, aminoglycosides and proton pomp inhibitors).

Measurement of calcium concentration:

Total serum calcium concentration was measured colorimetrically, whereas the serum ionized calcium concentration was measured using an ion-selective electrode method. Most patients were evaluated for calcium (total and ionized) after resuscitation at 1^{st} and 3^{rd} days of initiation of nutritional support and at 5 days after admission to ICU. Patients' albumin, calcium, magnesium, phosphorus and Blood urea and creatinine were measured.

Statistical analysis:

Data were analyzed using Statistical Package for the Social Sciences (SPSS, Version 25, Chicago, IL). The normality of data was assessed by Kolmogrov- Smirnove test. Quantitative variables were expressed as mean ± SD and qualitative variables as percent. We used Pearson correlation coefficient test to show the relationship between quantitative variables, especially total and ionized calcium. Independent t test was used to compare the variables between study groups. P value less than 0.05 was considered statistically significant. The $\chi 2$ test was performed to calculate differences in the proportion of categorical variables. Linear regression was used to describe changes of incidences over time. Values of $p < 0.05$ were considered to indicate statistical significance. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. P-values less than 0.05 (5%) was considered to be statistically significant. $P > 0.05$: Non-significant (NS), $P < 0.05$: Significant (S) and $P < 0.01$: Highly significant (HS).

RESULTS

The present study included 310 patients who were admitted to ICUand their calcium level was measured. The mean age of the studied cases was 50.58±14.31 years ranging from 22 to 80 years ,

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

51% were females and mean duration of ICU admission was 7.12±2.45 days ranging from 3 to 14 days **(Table 1)**. About 41% of the cases developed hypocalcemia on the third day of follow up and 59% of the studied cases developed hypocalcemia on the 5th day of follow up **(Figure 1)**. The current demonstrate that 40% of the studied cases were admitted to ICU due to sepsis and septic shock, 16% polytrauma , 10% respiratory failure, 10% post-operative monitoring , 6% with ICH , 6% with uncontrolled HTN, 4%with ischemic stroke, 2% pancreatitis , 2% dehydration & electrolyte imbalance , 2% DKA and one case due to organophosphorus poisoning and 1% rhabdomyolysis **(Figure 2)**.

The mean GCS was 11.79±2.16 ranging from 6 to 15 ,mean APACHE2 score was44.25±18.7 ranging from 2 to 50, mean creatinine 1.64±1.36 ranging from 0.5 to 6.3 , mean Urea 43.22±41.6 ranging from 12 to 170 , mean albumin 3.43±.64 ranging from 2 to 5, mean Ph 3.46±.5 ranging from 2.6 to 4.5 and mean Mg was 1.88±.29ranging from 1.2 to 2.6 **(Table 2)**. The present study showed 82% of the studied cases were treated with heparin, 79% with PPI , 21% diuretics and 18% aminoglycosides **(Figure 3)**. There is statistically significant negative correlation between GCS score and Ca total and ionized at 3rd day(r=-0.231 , p=0.021) and (r=-0.313 , p=0.002) **(Figure 4 &5)**.

Table (1): demographic characteristics and duration of ICU admission of the studied cases:

	total number=100
Age/years **Mean ±SD** **Range**	 50.58±14.31 (22.0-80.0)
Sex n(%) **Male** **Female**	 49(49.0%) 51(51.0%)
Duration of ICU stay/days **Mean ±SD** **Range**	 7.12±2.45 (3.0-14.0)

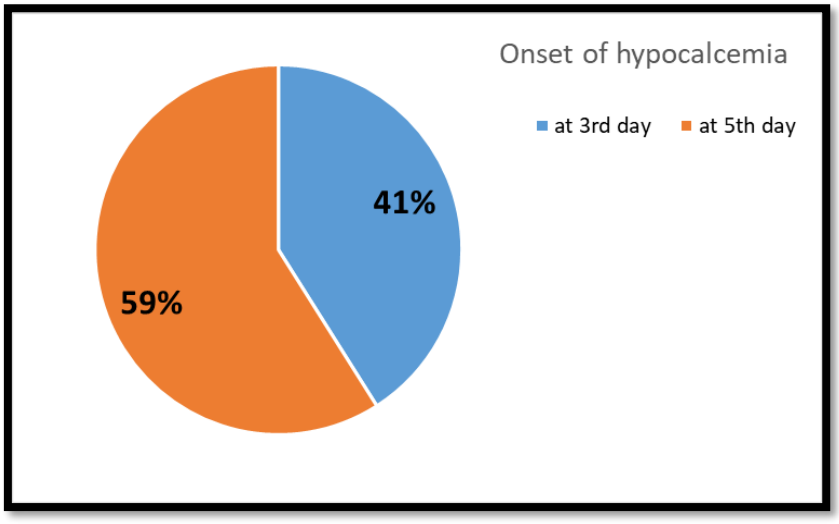

Figure (1): showing hypocalcemia onset among studied cases

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

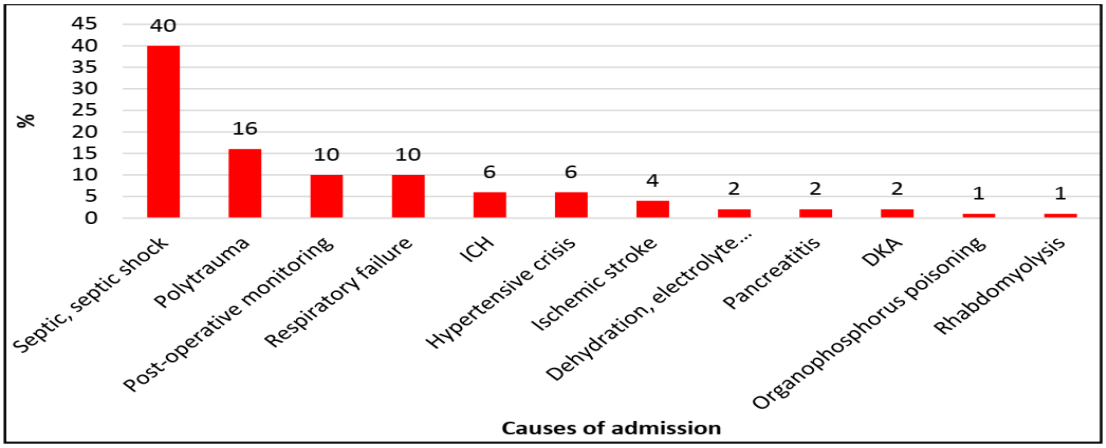

Figure (2): causes of ICU admission among studied cases

Table (2): Glasgow coma score and laboratory findings among studied cases

	total number=100	
	Mean±SD	Range
GCS	11.79±2.16	(6.0-15.0)
APACHE score	44.25±18.7	(2-50)
Serum creatinine	1.64±1.36	(0.5-6.3)
Serum Urea	43.22±41.60	(12.0-170.0)
Albumin	3.43±0.64	(2.0-5.0)
Ph	3.46±0.50	(2.6-4.5)
Mg	1.88±0.29	(1.2-2.6)
Ca(total)	8.2±.2	(8-8.5)
Ca(ionized)	4.2±.17	(3.9-4.14)

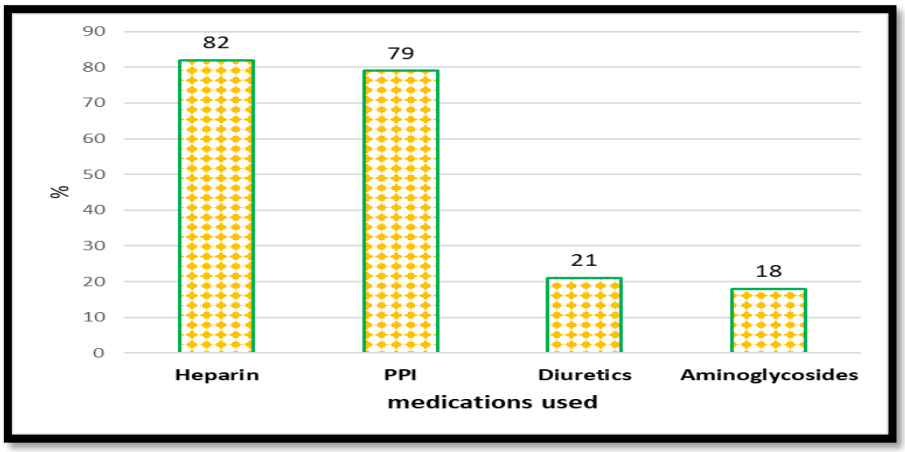

Figure (3): Distribution of the studied cases according to types of medications used

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

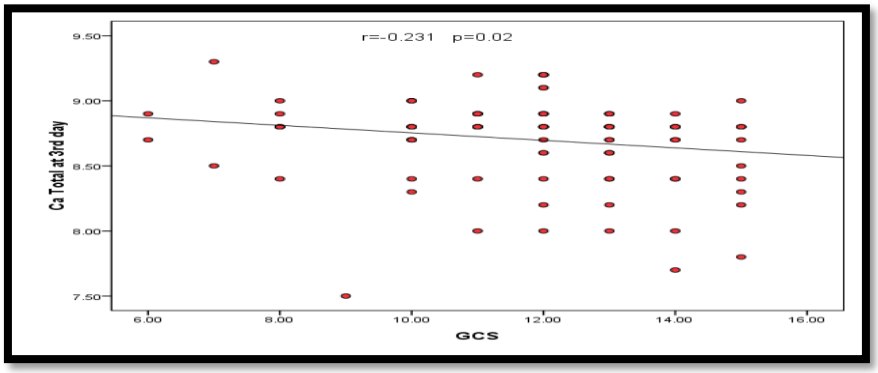

Figure (4): Scatter diagram showing correlation between GCS and Ca total at 3rd day

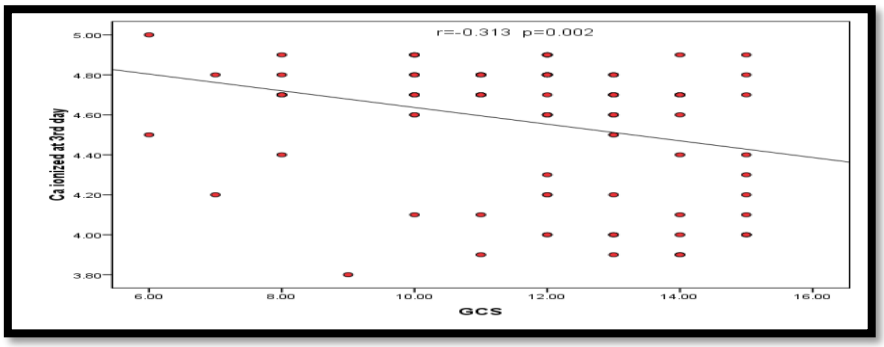

Figure (5): Scatter diagram showing correlation between GCS and Ca ionized at 3rd day

DISCUSSION:

Hypocalcemia is defined as a reduction in ionized serum calcium (Ca) less than 4.7 mg /dl concentration. Hypocalcemia is a common derangement in both medical and surgical patients requiring intensive care **(6)**. Several mechanisms have been shown for hypocalcemia in critically ill patients, such as proinflammatory biomarkers end organ resistance to PTH, extra and intra cellular redistribution of calcium ion, suppression of PTH secretion, and catecholamine release in critically ill patients **(3)**.

The study was conducted over a period of six month and included 100 patients for early prediction of cases of hypocalcemia for better management of patients at surgical intensive care unit of Zagazig University Hospitals/

In this study, the incidence of hypocalcemia was 41% in 3rd day of admission and 59% in 5th day of admission. In an analysis of 12 studies performed between 1988 and 2014 results reported the incidence of hypocalcemia in critically ill patients ranges from 50-88% **(3)**, Which comes in consistency with other studies that reported wide range from 15% to 88% **(Ahmed et al.(7); Ardehali et al. (8); Thongprayoon et al.(9))**.

In our study, distribution of studied cases was sepsis ,septic shock 40%(40 cases), poly trauma 16%(16 cases), post operative monitoring 10%(10 cases) and respiratory failure 10%(10 cases). the patients with hypocalcemia there were 36.7% females (n=18) and 45.1% males (n=23). Gender was not a significant risk factor for the development of 3rd day hypocalcemia.

This came in accordance with **Sanaie et al.(10)** who showed that there was no difference in the ionized, total, and corrected calcium concentrations between males and females patients admitted into ICU in their study, so they concluded that sex did not have any effect on different calcium parameters.

When it comes to the drugs incriminated in hypocalcemia development, only aminoglycosides intake was a significant risk factor for the development of such complication ($p = 0.014$). PPI, heparin and diuretics were not significant.

In line with our findings, there is evidence that the use of aminoglycosides and capreomycin causes renal wasting of electrolytes, including potassium, magnesium, and calcium **(11)**.

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

Regarding PPI in the previous literature, PPI-induced hypomagnesaemia was first recognised in 2006, with a report of two patients developing severe magnesium deficiency, in addition to hypocalcaemia and hypokalaemia, whilst on long-term PPI treatment **(12)**. Another review published in 2016 confirmed the increased risk of hypocalcemia with prolonged PPI use **(13)**.

Sepsis is a well-recognized risk factor for hypocalcemia. In nonseptic, critically ill adults, hypocalcemia (defined as ionized calcium <1.16 mmol/L) has also been recognized **(14)**.

Our findings that showed sepsis is a significant risk factor for hypocalcemia, as it was encountered in 55% of the hypocalcemic patients at 3rd day. Our study showed that respiratory failure was a risk factor for the development of that complication (p = 0.03). The occurrence of acute lung injury associated with hypercalcemia has rarely been reported and the mechanisms are unknown **(15)**.

In our study, APACHE score was a significant risk factor for hypocalcemia (p = 0.02).In the another study, APACHE-II scoring has shown increasing trend with decreasing Ca on admission. However, the mean APACHE-II score in moderately and severely hypocalcaemic patients were not much different (21.72±6.37 versus 22.34±7.53) **(16)**.

In our study, the duration of ICU stay was not a significant risk factor for hypocalcemia. This came in contrast with **(17)** showed that the median duration of ICU stay in cases with hypocalcemia was 9 days with range between 4 and 19 days which was longer as compared with the normocalcemic group.

CONCLUSION

Hypocalcemia is a frequent complication that could be encountered in the critically ill patients.Based on our findings incidence rate of hypocalcemia at 5th day of ICU admission is (59%) which is larger than that at 3rdday(41%) .

No Conflict of interest.

REFERENCES

1- **Liamis, G., Milionis, H. J., Elisaf, M.** A review of drug-induced hypocalcemia. Journal of bone and mineral metabolism,2009; 27(6), 635-642.
2- **Burchard KW, Gann D S,Colliton, J etal.** Ionized calcium, parathormone, and mortality in critically ill surgical patients. Annals of surgery1990;212(4), 543 .
3- **Aberegg, S. K.** Ionized calcium in the ICU: should it be measured and corrected?. Chest,2016; 149(3), 846-855.
4- **Naafs, M. .** Hypocalcemia in the Critically Ill: A Mini-Review. Endocrinol Metab Int J,2017; 5(4), 00130.
5- **Kelly, A., & Levine, M. A..** Hypocalcemia in the critically ill patient. Journal of intensive care medicine,2013; 28(3), 166-177.
6- **Duval M, Bach-Ngohou K, Masson D,etal.** Is severe hypocalcemia immediately life threatening? Endocrine connections2018; 7(10), 1067-1074 .
7- **AhmedA, AzimA, GurjarM,et al.** Hypocalcemia in acute pancreatitis revisited. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine,2016**;**20 (3) - 173 .
8- **Ardehali, S. H., Dehghan, S., Baghestani, A. R., Shariatpanahi, Z. V. (2018).** Association of admission serum levels of vitamin D, calcium, Phosphate, magnesium and parathormone with clinical outcomes in neurosurgical ICU patients. Scientific reports, 8(1), 1-8.
9- **Thongprayoon C, Cheungpasitporn W, chewcharat A, et al.**Hospital mortality and long-term mortality among hospitalized patients with variousadmission serum ionized calcium levels. Postgraduate Medicine2020;1-6 .
10- **Sanaie S, Mahmoodpoor A, Hamishehkar H, et al.**Association Between Disease Severity and Calcium Concentration in Critically Ill Patients Admitted to IntensiveCare Unit. Anesthesiology and pain medicine,2018.
11- **Varma, T., Saini, A., Panchani, R., et al.** Two unusual cases of severe recalcitrant hypocalcemia due to aminoglycoside-induced hypomagnesemia. Indian journal of endocrinology and metabolism(2013); 17(Suppl1): S206.

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

12- **Epstein M, McGrath S and Law F.** Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. New England Journal of Medicine(2006); 355(17): 1834-1836.
13- **Sivakumar J.** Proton pump inhibitor-induced hypomagnesaemia and hypocalcaemia: case review. International journal of physiology, pathophysiology and pharmacology(2016); 8(4): 169.
14- **Zivin JR, Gooley T, Zager RA, et al.** Hypocalcemia: a pervasive metabolic abnormality in the critically ill. American journal of kidney diseases2001: 37(4): 689-698 .
15- **Hsu YH and Chen HI.** Acute respiratory distress syndrome associated with hypercalcemia without parathyroid disorders. Chin J Physiol(2008); 51;641-651
16- **Dey S, Karim HR, Yunus M, et al.** Relationship of on Admission Hypocalcaemia and Illness Severity as Measured by APACHE-II and SOFA Score in Intensive Care Patients'. Journal of clinical and diagnostic research: JCDR(2017); 11(3): UC01.
17- **Steele, T., Kolamunnage-Dona, R., Downey, C., Toh, C. H., & Welters, I. (2013).** Assessment and clinical course of hypocalcemia in critical illness. Critical Care, 17(3), 1-10.