Research Article

Assessment of Ionized Calcium Levels in Various Acid Base Disorders in ICU Patients

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ABSTRACT

Hypocalcemia is very common in critically ill patients and ionized calcium levels are essential to analyze the calcium homeostasis because abnormal protein levels and acid base disturbances commonly seen in them influence the total calcium levels. Ionized calcium concentration values change inversely to pH values. The aim of the current research study is to analyze the ionized calcium levels in various acid base disorders in I.C.U patients. 212 arterial blood samples were collected and analysed using ABG analyser. ABG parameters like pH, pCO2, HCO3 and ionized calcium values were noted. Standard base excess, ratio between HCO3 and carbonic acid (HCO3/H2CO3) and calculated Ionized calcium (at pH 7.4) were calculated for all the samples. Arterial blood gas analysis revealed 25 normal cases, 9 respiratory acidosis, 55 respiratory alkalosis, 39 metabolic acidosis, 33 metabolic alkalosis and 51 mixed disorder cases. Acid base disorders are divided into 6 groups based on the ionized calcium levels namely ≤1 mg/dl, >1.0 ≤ 2.0 mg/dl, >2.0 ≤ 3.0 mg/dl, >3.0 ≤ 4.0 mg/dl, >4.0 ≤ 4.4 mg/dl and >4.4 ≤ 5.4 mg/dl. Mean ± standard deviation is calculated for all the cases. Ionized calcium level is normal in only 4.245 % of the total 212 cases. Low ionized calcium level is seen in critically ill patients irrespective of the acid base status. The relationship between pH, HCO3, pCO2 and ionized calcium levels were graphically analysed.

Keywords: ionized calcium, critically ill patients, pH, acid-base disorders.

INTRODUCTION

Calcium is found in three different fractions in circulation namely protein-bound, anion-bound and free or"ionized" form. The amount of calcium in each of these fractions is dependent on the concentration of plasma proteins, anions and hydrogen ions. The serum calcium is bound with proteins like albumin, globulins and anions like phosphate, lactate, free fatty acids and citrate.[1,2] The free or ionized calcium pool accounts for 45-50 % of the total calcium in circulation which represents the biologically active fraction of a larger total amount in circulation.[1,2,3]

Measurement of total calcium levels is usually sufficient to assess the calcium homeostasis, but in patients with abnormal pH, protein and anion concentrations, total calcium levels may not reflect the true status so measurement of ionized calcium (iCa^{2+}) is required.[1, 2, 3]

Hypocalcemia is very common in critically ill patients and total calcium levels may not reflect the true status in them.[4] The two principal clinical situations in which total calcium concentration does not sufficiently accurately reflect ionized calcium activity are patient's with abnormal serum protein concentration and those with acid-base disturbances which is clearly depicted in the below table.[1-5]

Clinical situations		Calcium Concentration		
		Protein bound form	Ionized form	Total
Changes in Protein levels	Increased	Increased	**Unchanged**	Increased
	Decreased	Decreased	**Unchanged**	Decreased
Changes in pH values	Decreased **(Acidic)**	Decreased	Increased	**Not Affected**
	Increased **(Alkaline)**	Increased	Decreased	**Not Affected**

The amount of calcium bound by serum protein is directly proportional to protein concentration. If serum protein concentration increases, then the concentration of protein-bound calcium and therefore total calcium concentration also increases. Conversely, if plasma protein concentration decreases, total plasma calcium level also decreases.[1, 2]

Changes in protein concentration (most significant is albumin) affects the total calcium levels but not the ionized calcium, the biochemically important parameter for clinicians which remains essentially unchanged.[1,2]

There are some formulae for estimation of corrected total calcium concentration to minimize the effect of abnormal serum protein concentration on total calcium level but none of them accurately reflect the ionized calcium level

because the calcium binding in a particular patient is multifactorial.[6, 7, 8]

Ionized calcium concentration is strongly influenced by pH. Both the ionized calcium (iCa^{2+}) and hydrogen ions compete for the same negatively charged binding sites on the protein molecules and this binding is pH dependent. Alkalosis, an increase in pH (decreased hydrogen ions), promotes increased protein binding, which decreases free calcium levels. Acidosis (Increased hydrogen ions), on the other hand, decreases protein binding, resulting in increased free calcium levels. Ionized calcium values change inversely to pH. The magnitude of change is 0.05 mmol/L per 0.1 pH change. There is only a shift of calcium from one fraction to another causing clinically significant change in calcium status but the total calcium concentration is not affected which remains unchanged.[1, 2, 5]

Simple acid base disorder is the presence of any one of the four disorders like metabolic acidosis, metabolic alkalosis, respiratory alkalosis and respiratory acidosis with appropriate renal or respiratory compensation for that disorder. If the compensation is not appropriate, then it may indicate a second acid-base disorder. Mixed acid-base disorder indicates simultaneous presence of more than one acid base disorder and it can be suspected from a lesser or greater than expected compensatory mechanisms (respiratory or renal).[9, 10]

The current research study is focussed to determine the serum ionized calcium levels in critically ill patients for various acid-base disorders.

MATERIALS AND METHODS

212 arterial blood gas analysis samples were collected for the past two months at Shri Sathya Sai Medical College and Research Institute. Strict precautions were taken to avoid pre-analytical errors and the samples were analyzed using ABG Analyzer GEM PREMIER 3000. Arterial Blood Gas Analysis data were collected and the consistency of the ABG report was checked by using the Modified Henderson Equation.[11, 12]

The following Pre-analytical errors that may result in abnormal ionized calcium levels had been strictly avoided. Haemolysis results in false low ionized calcium values. Prolonged use of a tourniquet can increase lactate production, thereby lowering the pH and falsely increasing the amount of iCa^{2+}. Significant time delay between collection and iCa^{2+} measurement can cause an apparent hypercalcemia due to metabolic activity (pH decrease).Once collected, the pH of a blood sample may decrease (acidic) from cell metabolism, acidic pH decreases protein bound calcium and increases ionized calcium levels. Loss of pCO_2 from the collected sample increases pH, so alkaline pH increases protein bound calcium and decreases ionized calcium levels.

Correct volume of blood was sampled to achieve correct heparin concentration and that blood and anticoagulant were well mixed immediately after sampling to avoid false low ionized calcium levels.[1,2] The main parameters like measured pH, pCO_2, HCO_3values were noted. Carbonic acid concentration was calculated from pCO_2. The ratio between HCO_3 and carbonic acid was calculated and represented by HCO_3/H_2CO_3.[11, 12]

Calculation of Carbonic Acid Concentration

The carbonic acid concentration (mmol/L) was calculated by the given formula.

$$H_2CO_3=0.03 \text{ X } pCO_2$$

Calculation of HCO_3/H_2CO_3

Carbonic acid was derived from pCO_2 values and the ratio between HCO_3 and carbonic acid (HCO_3/H_2CO_3) was found.

Calculation of Standard Base excess (Base Excess of the extra cellular fluid)

Std Base Excess (STD BE) is calculated by the given formula.[13]

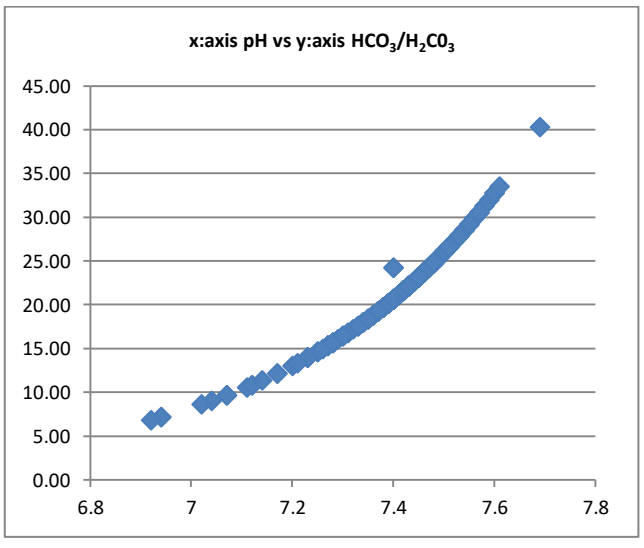
Std Base Excess (STD BE) = HCO_3 – 24.8 + 16.2 (pH -7.4)

Calculation of Corrected Ionized Calcium (at pH 7.4)

Corrected ionized calcium is calculated by the given formula.[1,2, 13]

Corrected ionised calcium = Measured iCa x (1 - 0.53 x (7.4-pH))

Delta calcium is the difference between ionized calcium and calculated calcium (at pH: 7.4)

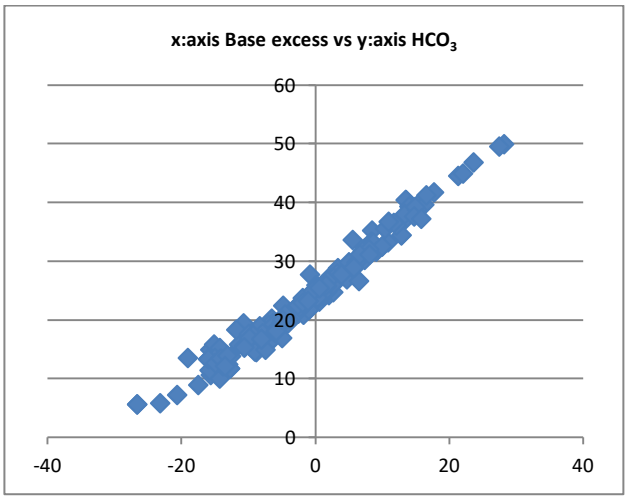


Graph 1: pH vs HCO_3/H_2CO_3

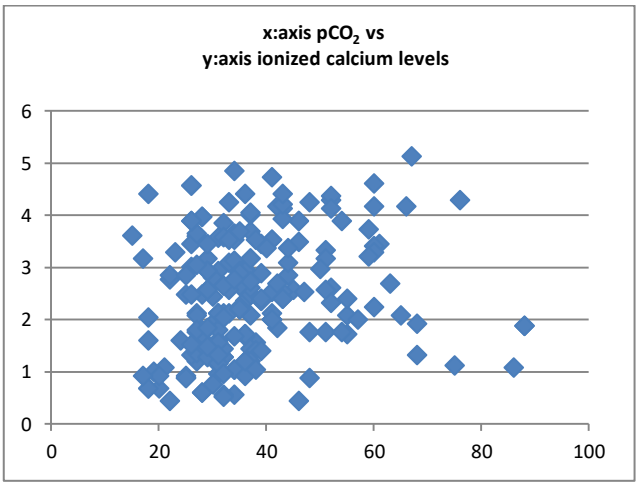
Table 1: Ionized Calcium Levels In Various Acid Base Disorders

The reference range of ionized calcium is >4.4 ≤ 5.4 mg/dl.

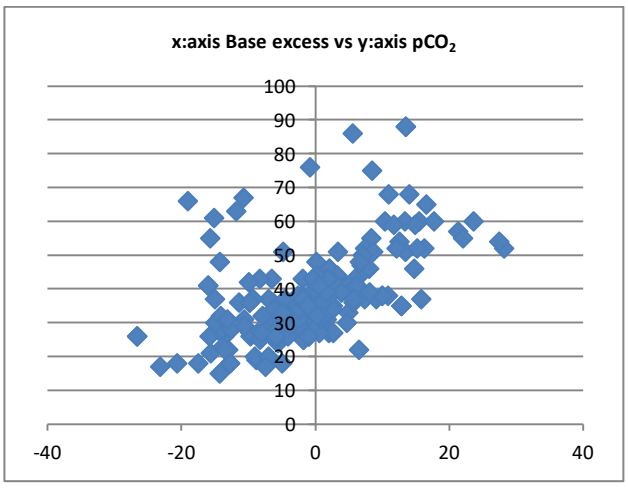
Ionized calcium Levels mg/dL	Normal cases	Respiratory acidosis	Respiratory alkalosis	Metabolic acidosis	Metabolic alkalosis	Mixed disorder	TOTAL cases and percentage
Number of cases	25	9	55	39	33	51	212 **(100%)**
Group 1 ≤1	1	0	9	2	1	8	21 **9.91 %**
Group 2 >1.0 ≤ 2.0	4	3	19	17	8	9	60 **28.30 %**
Group 3 >2.0 ≤ 3.0	14	0	14	8	8	19	63 **29.72 %**
Group 4 >3.0 ≤ 4.0	3	2	10	8	11	10	44 **20.75 %**
Group 5 >4.0 ≤ 4.4	2	3	2	1	4	3	15 **7.075 %**
Group 6 (Normal Range) **>4.4 ≤ 5.4**	1	1	1	3	1	2	9 **4.245 %**
Mean	**2.685**	**3.236**	**2.176**	**2.346**	**2.778**	**2.45**	**2.45**
Standard Deviation	0.892	1.351	1.11	1.14	1.013	1.13	1.113



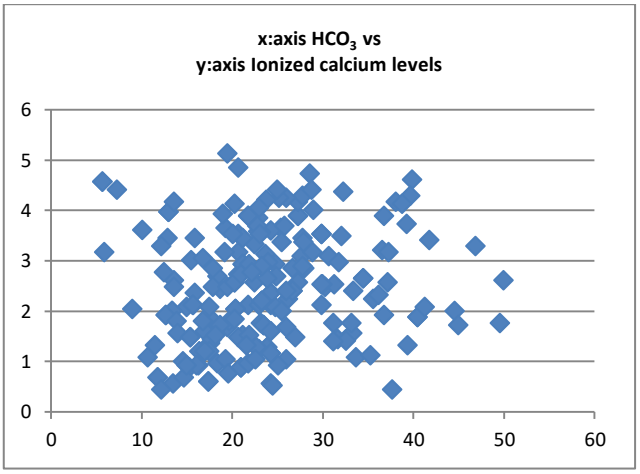
Graph 2: Base excess vs HCO_3



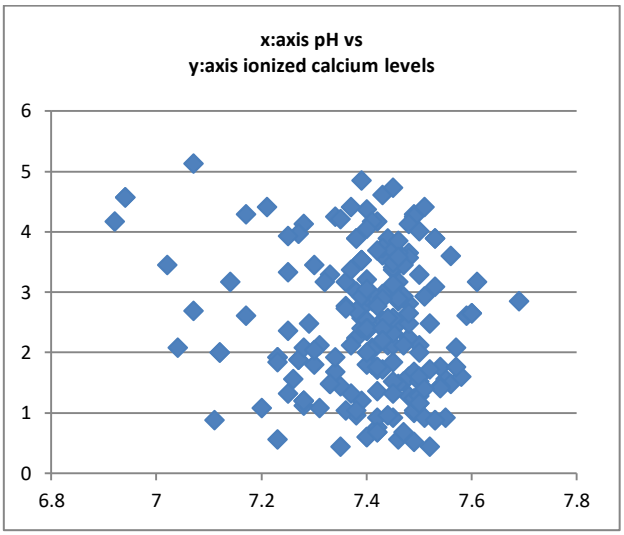
Graph 4: pCO_2 vs ionized calcium levels



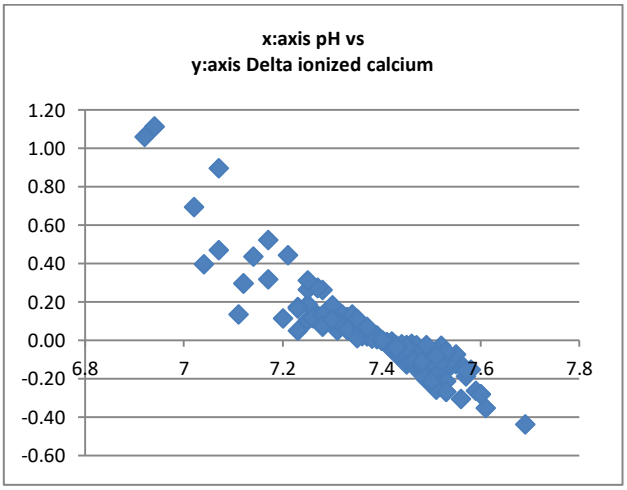
Graph 3: Base excess vs pCO_2



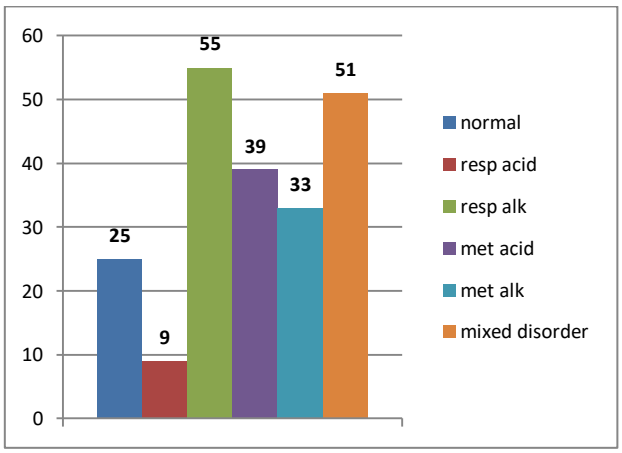
Graph 5: HCO_3 vs ionized calcium levels



Graph 6: pH vs ionized calcium levels



Graph 7: pH vs Delta ionized calcium levels



Graph 8: Distribution of various acid base disorders of the Total 212 cases

DISCUSSION

Low ionized calcium level is common in critically ill patients and majority of these patients do not have any underlying disease of calcium homeostasis.[4] Abnormal low ionized calcium levels are likely a marker of disease severity of critical illness and most often normalize spontaneously in the resolution of the primary disease process. Ionized calcium values in acutely ill patients represent an adaptive and protective response.[14,15,16] Earlier studies identified ionized calcium levels as a risk factor for mortality in i.c.u patients and the calcium levels normalize spontaneously especially in survivors. Some studies pointed out that the homeostatic set point for ionized calcium differs in health and disease. Also, Ionized calcium is refractory to treatment in i.c.u patients.[16] Studies done in paediatric patients showed that hypocalcemia frequently seen in critically ill children is associated with raised levels of calcitonin and Parathyroid hormone (PTH) and the mechanism for the increase in calcitonin is unknown.[17, 18]

The aim of the current research study is to determine the serum ionized calcium levels in i.c.u patients for various acid-base disorders. The reference range of ionized calcium is >4.4 ≤ 5.4 mg/dl. Ionized calcium levels were measured in the total 212 samples and divided into **six** groups based on the ionized calcium levels for various acid base disorders.(Group 1: ≤1 mg/dL, Group 2: >1.0 ≤ 2.0 mg/dL, Group 3: >2.0 ≤ 3.0 mg/dL, Group 4: >3.0 ≤ 4.0 mg/dL, Group 5: >4.0 ≤ 4.4 mg/dL and Group 6 (Normal range): >4.4 ≤ 5.4 mg/dL) were clearly shown in table 1.

The correlation between pH and ratio HCO_3/H_2CO_3, base excess and bicarbonate and base excess and pCO_2 were clearly shown in the graphs 1, 2 and 3 respectively. The relation between pCO_2, bicarbonate, pH and ionized calcium for all the 212 samples were analyzed and shown in the graphs 4,5 and 6 respectively which depicted there is no clear correlation individually for each sample. Delta calcium is the difference between ionized calcium and calculated calcium (at pH: 7.4). The relation between pH and delta calcium shown in the graph 7 obviously depict that it is positive for acidic and negative for alkaline pH. Distribution pattern of various acid base disorders of the total 212 samples is clearly shown in the bar graph 8.

The study shows that ionized calcium level is normal in only 4.245 % of the total cases. Low ionized calcium level is seen irrespective of the acid base status. Mean ± standard deviation for the ionized calcium level for each of the acid base disorders was calculated and shown in the table 1. Mean ± standard deviation for the total 212 sample is 2.45 ± 1.113 which clearly shows that ionized calcium levels are commonly decreased in critically ill patients irrespective of the acid base status.

CONCLUSION

The levels of ionized calcium are frequently decreased in critically ill patients irrespective of the acid base disturbances. Measurement of ionized calcium levels and monitoring them in critically ill patients may help in assessing the severity of the illness and predicting the prognosis of the patients.

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