The Value of Initial Ionized Calcium as a Predictor of Mortality and Triage Tool in Adult Trauma Patients

Ionized hypocalcemia is a common finding in critically ill patients, but the relationship between ionized hypocalcemia and mortality risk in trauma patients has not been well established. The aim of this study was to assess the usefulness of initial ionized calcium (iCa) in predicting mortality in the trauma population, and evaluate its superiority over the three other triage tools: base deficit, systemic inflammatory response syndrome (SIRS) score, and triage-revised trauma score (t-RTS). A prospective and retrospective study was performed on 255 consecutive trauma patients admitted to our Emergency Medical Center from January to December, 2005, who underwent arterial blood gas analysis. Multivariate logistic regression analysis confirmed iCa (≤ 0.88 mM/L), low Glasgow coma scale score, and a large transfusion amount to be significant risk factors associated with mortality (p<0.05). The sensitivities of iCa, base deficit, SIRS score, and t-RTS were 82.9%, 76.4%, 67.1%, and 74.5%, and their specificities were 41.0%, 64.1%, 64.1%, and 87.2%, respectively. Receiver operating characteristic curve analysis determined the areas under the curves of these parameters to be 0.807 ± 0.062, 0.736 ± 0.056, 0.694 ± 0.059, and 0.875 ± 0.043, respectively (95% confidence interval). Although initial iCa (≤ 0.88 mM/L) was confirmed as a significant risk factor associated with mortality, it exhibited a poorer discriminative power for mortality prediction than other predictors, especially t-RTS.

Key Words: Trauma; Hypocalcemia; Mortality; Triage

INTRODUCTION

Calcium is a divalent cation involved in many critical cellular processes. Several biochemical and physiological studies have demonstrated the importance of calcium in regulating vascular and myocardial contraction, activating membrane receptors during cellular signal transduction, releasing many hormones by exocytosis, controlling several transport processes and promoting thrombus formation as co-factor IV (1-4). 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; and 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 (5).

Hypocalcemia has been reported in critically ill patients, most commonly in association with septic condition (6). It may vary from an asymptomatic biochemical abnormality to a severe life-threatening condition depending on the duration, severity, and rapidity of development. The causes of hypocalcemia arise either from increased loss of calcium from the circulation or from insufficient entry of calcium into the circulation. It is well recognized that all pathophysiological changes in shock and trauma have their basis at the cellular and molecular levels. A recent study observed hypocalcemia in 88% of critically ill patients, and a correlation between decreased calcium levels and increased mortality (6). However, the relationship between hypocalcemia and mortality risk in trauma patients has not been well defined. Base deficit, systemic inflammatory response syndrome (SIRS) score, and triage-revised trauma score (t-RTS) are three well-known predictors for the mortality in trauma patients as well as triage tools. Therefore, the purpose of the present study was to assess the usefulness of initial iCa in predicting mortality, and evaluate its superiority over these three triage tools in the trauma population.

MATERIALS AND METHODS

Patient population

Arterial blood gas analysis (ABGA) was performed on all
trauma patients satisfying the following inclusion criteria in our Emergency Medical Center (EMC): 1) altered mental status (Glasgow coma scale [GCS] score <13); 2) hemodynamic instability (initial systolic blood pressure [SBP] <90 mmHg or heart rate >100 beats per minute); 3) respiratory compromise (<10 or >29 breaths per minute); 4) severe craniofacial fractures with extensive hemorrhage and/or airway compromise; 5) flail chest; 6) any penetrating injuries to the head, neck, torso, or extremities proximal to the elbow and knee; 7) limb paralysis; 8) amputation proximal to wrist and ankle; 9) two or more proximal long bone fractures; 10) pelvic bone fractures; 11) falls of >6 meters; or 12) high speed auto crash, roll-over, or pedestrian run over. The following patients were excluded in this study: 1) more than 24 hr of time interval from injury onset to arrival on EMC; 2) known underlying liver cirrhosis; 3) known underlying chronic renal failure; 4) known parathyroid disease; 5) current treatment for malignancy; and 6) age younger than 16 years. Of 278 consecutive trauma patients admitted to our EMC from January to December, 2005 who underwent ABGA, 23 lost to follow-up (18 were transferred to other hospitals and 5 had omitted data). The medical records of the remaining 255 patients were carefully examined pro- and retrospectively.

Data collection and assessment

Arterial blood gas, complete blood cell count, GCS score, and vital signs were measured to obtain iCa, base deficit, SIRS score, and t-RTS. ABGA was performed by an emergency physician within 10 min after arrival at the emergency department (Blood Gas Analyzer Gem Premier 3000, Lexington, MA, U.S.A.). Serum pH, iCa, arterial oxygen pressure (PaO2), arterial carbon dioxide pressure (PaCO2), serum bicarbonate, base deficit, and arterial oxygen saturation (SaO2) levels were automatically measured by ABGA. Of the two values of iCa, i.e., uncorrected and corrected to pH=7.40, presented in the ABGA results, the former was used for mortality prediction. The latter was automatically calculated by following equation: corrected iCa= uncorrected iCa × 10-(0.178 × [PaCO2/40]-log(10)). The measurement’s coefficient of variation was 2.5% and the iCa normal range was 1.15-1.35 mEq/L. SIRS score and t-RTS were calculated based on the original article. SIRS score was calculated by using body temperature, pulse rate, respiratory rate or PaCO2, and white blood cell count, and ranged from 0 to 4. SIRS was defined by a score of two or more (7). The t-RTS is a compound indicator consisting of GCS score, SBP, and respiratory rate, and ranges from 0 to 12 (8). In addition, the following data were obtained in this study: age, sex, mechanism of injury, amount of intravenous fluid (crystalloid or colloid) administered in the prehospital phase of care, transfusion amount (before and after arrival in the EMC), injury severity score (ISS), revised trauma score (RTS), emergency operation, infection, and survival. Most of the above data had been measured before discharge from the EMC and collected prospectively, but the following data had been done retrospectively: transfusion amount after arrival in the EMC, ISS and infection.

All the above factors were evaluated to be associated with mortality. Furthermore, the abilities of iCa and the other three indicators to predict mortality were compared in the following aspects. First, the areas under the curves (AUCs) on receiver operating characteristic (ROC) curve analysis of these indicators were obtained to assess their discriminative power for mortality prediction. Second, the sensitivities, specificities, and accuracies of these indicators were determined by constructing a contingency table according to survival after these indicators were transformed into dichotomous variables based on severity. SIRS score was easily converted into a dichotomous variable via the above definition (≥2). However, having no definite criteria on major trauma, the other indicators were assessed by obtaining the cut-off point with the best separation between survivors and non-survivors on ROC curve analysis.

Statistical analysis

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, U.S.A.) and MedCalc (MedCalc 9.3 version, Mariakerke, Belgium). Univariate analysis was performed by using the Student’s t test for continuous variables or the chi-square test for categorical variables. All variables found to be significant by univariate analysis then underwent multivariate logistic regression analysis. In addition, the amounts of intravenous fluid (crystalloid or colloid) and transfusion administered before arrival in EMC were adjusted for multivariate analysis because of the possible effect on iCa (9-11). The differences between the AUCs of iCa, base deficit, SIRS score, and t-RTS were determined by using the nonparametric method proposed by Hanley and McNeil (12). The differences between the sensitivities, specificities, and accuracies of these indicators were determined by using the McNemar test. All tests for significance were two-tailed with an alpha level of 0.05. Type I error was corrected by the Bonferroni’s method for comparisons of 3 or more variables.

RESULTS

The mean age of the study population was 47.2 ± 16.0 yr with a range from 16 to 90 yr. Males predominated at 76.5% (195 patients). The mean ISS was 18.5 ± 9.2 (range 4-75) and mean RTS was 7.08 ± 1.39 (range 0-7.84). Blunt trauma was the predominant mechanism of injury at 95.3% (243 patients), with penetrating injury accounting for only 4.7%. Traffic accident injuries were the most common at 60.0%,
followed by injuries due to falls at 25.5%, other blunt traumas at 9.8%, and stab injuries 4.7%. There was no gunshot wound in this population.

Survivors predominated (n=216) and there were 39 mortalities. Age, sex, and mechanism of injury were not associated with mortality (Table 1). Univariate analysis confirmed the following to be correlated with mortality: iCa, GCS score, serum bicarbonate, base deficit, SaO2, initial SBP, pulse rate, body temperature, SIRS score, t-RTS, emergency operation, transfusion amount, ISS, and RTS (p<0.05, Table 2). On ROC curve analysis, the iCa cut-off point for mortality prediction was 0.88 mM/L (Fig. 1). The patients were divided into three groups according to this iCa cut-off point and the recognized cut-off point for normal condition: 1) normal iCa concentration (≥1.15 mM/L), 2) mild ionized hypocalcemia (0.89-1.14 mM/L), and 3) severe ionized hypocalcemia (≤0.88 mM/L). The frequencies of these groups were 7 (2.7%), 195 (76.5%), and 53 (20.8%), respectively. The severity of ionized hypocalcemia was significantly associated with mortality (p<0.003, Table 3). The cut-off points of the base deficit and t-RTS were -6.3 mM/L and 11, respectively. The cut-off point of SIRS score was determined by the inherent SIRS score definition of 2 or more. Based on these cut-off points, the four indicators were transformed into dichotomous variables, after which the other significant factors as well as amounts of intravenous fluid and blood transfusion administered in the pre-hospital phase were adjusted for multivariate analysis. Multivariate logistic regression analysis confirmed iCa (≤0.88 mM/L), GCS score, and transfusion amount after arrival in the EMC to be associated with mortality (p<0.05, Table 4).

The AUC of t-RTS for mortality prediction was 0.875 ± 0.043 (95% confidence interval [CI]) and it exhibited excel-

| Table 1. Demographic characteristics and mechanism of injury | | | |
| --- | --- | --- | --- |
| Factors | Survivors (n=216) | Non-survivors (n=39) | p value |
| Age | 47.2±16.2 | 47.0±14.8 | NS |
| Sex | | | |
| Male | 166 | 29 | NS |
| Female | 50 | 10 | |
| Mechanism | | | |
| Traffic accident | 128 | 25 | |
| Fall | 54 | 11 | NS |
| Stab | 12 | 0 | |
| Others* | 22 | 3 | |
| Data are expressed as mean and standard deviation or frequencies. The significance was determined by Student’s t-test or chi-square test. * Other blunt traumas included human violence, industrial accident, etc. |

| Table 2. Significant factors associated with mortality on univariate analysis | | | |
| --- | --- | --- | --- |
| Factors | Survivors (n=216) | Non-survivors (n=39) | p value |
| Ionized calcium (mM/L) | 0.97±0.12 | 0.93±0.12 | 0.035 |
| GCS score | 13.2±2.7 | 7.3±4.1 | 0.000 |
| Bicarbonate (mM/L) | 21.2±3.7 | 17.6±5.1 | 0.000 |
| Base deficit (mM/L) | -3.8±4.4 | -8.4±6.4 | 0.000 |
| Oxygen saturation (%) | 93.5±7.2 | 85.3±21.3 | 0.021 |
| Initial systolic BP (mmHg) | 118.5±27.2 | 97.4±49.0 | 0.012 |
| Pulse rate | 87.6±17.8 | 101.2±25.1 | 0.002 |
| Body temperature (°C) | 36.40±0.37 | 36.26±0.30 | 0.036 |
| SIRS score | 1.1±0.9 | 1.8±0.8 | 0.000 |
| Triage-RTS | 11.5±0.9 | 8.5±2.9 | 0.000 |
| Emergency operation | | | |
| Yes | 74 | 24 | 0.001 |
| No | 142 | 15 | |
| Transfusion amount (unit)* | 1.2±2.7 | 4.5±5.3 | 0.000 |
| ISS | 17.1±8.1 | 26.5±10.3 | 0.000 |
| RTS | 7.45±0.78 | 5.01±2.05 | 0.000 |
| Data are expressed as mean and standard deviation or frequencies. The significance was determined by Student’s t-test or chi-square test. * Underwent after arrival in the emergency medical center. |

| Table 3. Mortality rates relative to ionized calcium levels | | | |
| --- | --- | --- | --- |
| | Survivors (n=216) | Non-survivors (n=39) | Mortality (%) | p value |
| Normocalcemia | 6 | 1 | 14.3 | |
| Mild hypocalcemia | 173 | 22 | 11.3 | 0.003 |
| Severe hypocalcemia | 37 | 16 | 30.2 | |
| Data are expressed as frequencies or percentage. | | | |
Dent discrimination. That of base deficit was 0.736 ± 0.056 (95% CI) with acceptable discrimination. Those of iCa and SIRS score were 0.607 ± 0.062 (95% CI) and 0.694 ± 0.059 (95% CI), respectively, with poor discrimination (Fig. 2). The AUC of iCa was not different from that of SIRS, but smaller than those of the other predictors (p<0.05). The AUC of t-RTS was the largest (p<0.01).

The sensitivities of iCa, base deficit, SIRS score, and t-RTS were 82.9%, 76.4%, 66.7%, and 76.5%, respectively (Table 5). The sensitivity of iCa was higher than that of SIRS score, but the specificity of iCa was lower than that of t-RTS (p<0.01).

**DISCUSSION**

Ionized hypocalcemia is a common finding in the intensive care unit (ICU), particularly in patients with sepsis, major trauma or pancreatitis (4, 6, 13). It has been shown to be of prognostic value due to its relation with mortality in critically ill patients (6, 10, 13-15). However, its cause in critically ill patients has not been well defined. Insufficient secretion or inhibited action of parathyroid hormone, decreased vitamin D3 production, and increased calcium deposition, both intra- and extra-cellularly, have all been suggested to be involved in the pathogenesis of hypocalcemia (4).

Hypocalcemia has potentially harmful effects clinically. In blood coagulation and the cardiovascular system, calcium plays a critical role, but few studies have attempted to clearly define the consequences of low iCa concentrations such as compromised hemodynamics. The contractile function of the heart is compromised during hypocalcemia but rapid and reliable recovery is achieved by calcium administration (16). Frank cardiac failure and a prolonged QT interval have been observed at iCa levels of approximately 0.5 mM/L (17). In addition, blood coagulation may be compromised due to hypocalcemia at iCa levels of <0.6-0.7 mM/L (18).

Hastbacka and Pettila (19) measured iCa in a cohort of 941 consecutive, critically ill patients. They found ionized hypocalcemia (iCa <1.15 mM/L) in 85% of patients at ICU admission. In their study, they first defined the cut-off point for severe ionized hypocalcemia as 0.9 mM/L, but did not present clear evidence for this definition. We therefore performed ROC curve analysis to define severe ionized hypocalcemia clearly. Our study results supported an iCa cut-off point for mortality prediction of 0.88 mM/L, with a lower level indicating severe ionized hypocalcemia. As expected, our criterion of severe ionized hypocalcemia was similar to theirs. Vivien et al. (10) measured iCa in a cohort of 212 consecutive, severe trauma patients. They found mild (0.90-1.14 mM/L) and severe (<0.90 mM/L) ionized hypocalcemia in 64% and 10% of patients at hospital admission, respectively. Their study results indicated a progressive increase in mortality with decreasing iCa levels, in agreement with our own results (Table 3). In the present study, severe ionized hypocalcemia, low GCS score, and large transfusion amount received

### Table 4. Multivariate analysis of factors associated with mortality

| Factors                        | Coefficient | Odds ratio (95% CI) | p value |
|-------------------------------|-------------|---------------------|---------|
| Ionized calcium ≤ 0.88 mM/L   | 1.130       | 3.10 (1.11-8.62)    | 0.031   |
| Oxygen saturation (%)         | -0.036      | 0.96 (0.93-1.00)    | 0.076   |
| GCS                           | -0.395      | 0.67 (0.60-0.76)    | 0.000   |
| Transfusion amount*           | 0.116       | 1.12 (1.05-1.21)    | 0.001   |

GCS, Glasgow coma scale.
* Underwent after arrival in the emergency medical center.

### Table 5. Sensitivities, specificities, and accuracy rates of ionized calcium and other indicators in predicting mortality

|                      | Ionized calcium | Base deficit | SIRS score | Triage-RTS |
|----------------------|-----------------|-------------|------------|------------|
| Sensitivity          | 82.9            | 76.4        | 67.1*      | 74.5       |
| Specificity          | 41.0            | 64.1        | 64.1       | 87.2*      |
| Accuracy             | 76.5            | 74.5        | 66.7       | 76.5       |

Data are expressed as percentiles. The significance was determined by McNemar test with Bonferroni’s correction.
* p<0.01 compared with ionized calcium.

SIRS, systemic inflammatory response syndrome; RTS, revised trauma score.
after arrival in the EMC were significantly associated with mortality on multivariate logistic regression analysis. Such a correlation of severe ionized hypocalcemia to mortality was also shown by previous studies using multivariate analysis (19, 20).

Several studies have reported that iCa concentration might be influenced by intravenous fluid (crystalloid or colloid) or blood transfusion. Fulgenico et al. (9) reported that the amount of crystalloids administrated to the patient after brain death was significantly correlated with plasma ionized calcium concentration. Vivien et al. (10) demonstrated that the volume of colloids administered was significantly and negatively correlated with iCa concentration. Another study found that elevations in circulating citrate levels and speed of transfusion were correlated with decreases in iCa concentration during blood transfusion (11). Based on these reported findings, we included the amounts of these factors administrated in the prehospital phase of care in the multivariate regression analysis, even though they were not associated with mortality on univariate analysis. However, the result was the same as that of multivariate regression analysis with these factors excluded. This unexpected result was thought to be due to the lack of any significant association of iCa concentration with these factors on correlation analysis and/or to the small patient population underwent blood transfusion (eight cases) and colloid infusion (only one case) in the prehospital phase (data not shown).

As aforementioned, iCa must be a significant risk factor for mortality. However, this may not be reflected in a sufficient discriminative power of iCa for mortality prediction (21, 22). We therefore performed two discriminative analyses: 1) corresponding statistics of classification tabulations, i.e., sensitivities, specificities and accuracies; and 2) AUC by ROC analysis. Only one previous study by Hastbacka and Pettila performed such discriminative analyses for iCa mortality prediction (19). The discrimination of ROC analysis in their study was an AUC of 0.636 (95% CI 0.591-0.681), while the sensitivity and specificity of severe ionized hypocalcemia were 98% and 7% for mortality, respectively. This AUC result was in accordance with ours except for the sensitivity and specificity. The discrepancies of the sensitivities and specificities between the two studies seem to have been due to differences in patient selection: all subjects in our study were trauma patients, whereas only 3% in their study were.

We recently reported that base deficit, t-RTS, and SIRS score were associated with mortality and that the first two were significant mortality predictors, despite their different discriminative powers in the following order: t-RTS > base deficit > SIRS score (23). However, no study has compared the discriminative powers of ionized hypocalcemia and these predictors before the present study. In our study, using corresponding statistics of classification tabulations for mortality, the discriminative power of iCa was the same as or inferior to that of base deficit and t-RTS, except for SIRS score. Moreover, discrimination by ROC analysis for mortality prediction revealed that AUC of iCa was 0.607, which was considered a poor discrimination in general. On the other hand, the AUCs of base deficit (0.736) and t-RTS (0.875) represented acceptable and excellent discrimination, respectively, as in our previous study (23).

ABGA requires only one puncture for blood sampling and can be performed within a few minutes. All the obtained results including iCa and base deficit, can be easily utilized without any modification. However, SIRS score and t-RTS are not single factors, but are compound factors consisting of several factors that require certain modification by recoding. Therefore, the former have advantages of simplicity and quickness over the latter. In addition, the former shows little variation because they comprise instrument-measured data, whereas the latter may suffer from greater variation due to partial or complete human measurement, i.e., doctors, nurses, or emergency medical technicians. In a recent study, GCS score and its components, one of the three parts of the t-RTS compound indicator, were found to have only a moderate degree of interrater agreement (24). This result confirmed that human measurement might have more variation than instrumental measurement. Unfortunately, despite its several advantages, iCa suffered from the fatal disadvantage of a low discriminative power, which is the most important property for mortality predictor.

The limitation of this study was a possible selection bias in selecting the patient population, which may have resulted from the small sample size and the single center approach. Therefore, we suggest that a multi-center or randomized trial be conducted in the future to avoid these biases and confirm our results.

In conclusion, iCa was a significant risk factor associated with mortality, but with a poorer discriminative power for mortality prediction and triage than previous mortality predictors, especially t-RTS. The iCa predictor is a single factor, whereas t-RTS is a compound indicator consisting of three factors (GCS score, SBP, and respiratory rate) which have been recognized as mortality predictors. Considering the difficulty and complexity in measuring t-RTS, its superiority to iCa as a mortality predictor is understandable. If a new predictor combining iCa with the other significant factors known to be associated with mortality can be developed, we expect that it may be a superior mortality predictor than t-RTS.

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