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Effect of ionized calcium level on short-term prognosis in severe multiple trauma patients: a clinical study

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ABSTRACT

Background Hypocalcemia has been reported as an independent predictor of trauma mortality. We investigated the relationship between temporal variations in blood ionized calcium concentration (iCa) and prognosis in severe trauma patients who underwent massive transfusion protocol (MTP).

Methods This single-center, retrospective, observational study investigated 117 severe trauma patients treated with MTP in the Department of Emergency Medicine and Critical Care, Saitama Medical Center, Saitama Medical University, between March 2013 and March 2019. Multivariate logistic regression analysis was performed, assigning pH-corrected initial and minimum blood ionized calcium concentration within 24 hours of admission (iCa_min), age, initial systolic blood pressure and Glasgow Coma Scale (GCS) score, and incidence of Ca supplementation as independent variables and 28-day mortality as dependent variable.

Results The logistic regression analysis identified iCa_min (adjusted OR 0.03, 95% CI 0.002 to 0.4), age (adjusted OR 1.05, 95% CI 1.02 to 1.09), and GCS score (adjusted OR 0.84, 95% CI 0.74 to 0.94) as significant independent predictors of 28-day mortality. The receiver operating characteristic analysis identified optimal cut-off value of iCa_min for predicting 28-day mortality as 0.95 mmoL/L (area under the curve 0.74).

Conclusion In the management of patients with traumatic hemorrhagic shock, aggressive correction of the iCa to maintain 0.95 mmol/L or higher within 24 hours of admission may improve short-term outcomes.

Level of evidence Therapeutic/care management, level III.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Calcium is an important component in the resuscitation of severe trauma patients.

⇒ Hypocalcemia on arrival is known to be associated with poor short-term prognosis and massive blood transfusions.

WHAT THIS STUDY ADDS

⇒ Minimum serum ionized calcium level taken within 24 hours after admission was associated with short-term prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Aggressive calcium correction may improve short-term prognosis for patients with traumatic hemorrhagic shock.

INTRODUCTION

In the acute management of patients with traumatic hemorrhagic shock, it is important to achieve early and reliable hemostasis and limit blood loss while avoiding the triad of traumatic death: hypothermia, acidosis, and coagulopathy.[1 2] In recent years, in addition to the triad of traumatic death, hypocalcemia has gained attention as a fourth factor that interacts with this triad to increase the risk of mortality.[1] Initial blood ionized calcium concentration at admission (iCa_ini) is reportedly associated with prehospital hypotension, need for blood transfusion, and even mortality.[3–6]

However, the relationship between temporal variations in blood ionized calcium concentration (iCa) after hospitalization and prognosis remains unclear. In this study, we also focused on the minimum blood ionized calcium concentration within 24 hours of admission (iCa_min) as a parameter reflecting temporal variations in iCa and examined the relationship between iCa_min and prognosis in patients treated with a massive transfusion protocol (MTP). The objective of this study was to clarify the relationship between temporal variations of iCa and 28-day mortality in patients with traumatic hemorrhagic shock receiving an MTP. We also aimed to determine the optimal cut-off value of iCa_min for predicting 28-day mortality and to define a target iCa as an index for correcting hypocalcemia in the acute management of patients with traumatic hemorrhagic shock.

PATIENTS AND METHODS

Study design

This study is a single-center, retrospective, observational study. The study was conducted at the Department of Emergency Medicine and Critical Care, Saitama Medical Center, Saitama Medical University (hereafter referred to as 'the institution').

Patient enrollment

Figure 1 shows a flow diagram of patient enrollment in the study. From March 1, 2013, to March 31, 2019, 4273 trauma patients were admitted to our hospital. Of these, 127 patients with an Injury Severity Score (ISS) of 16 or higher were treated with MTP after excluding 22 patients with cardiopulmonary arrest on arrival; of the 127 patients, 117 were enrolled in the study after excluding 10 patients with missing iCa data. All the 117 patients

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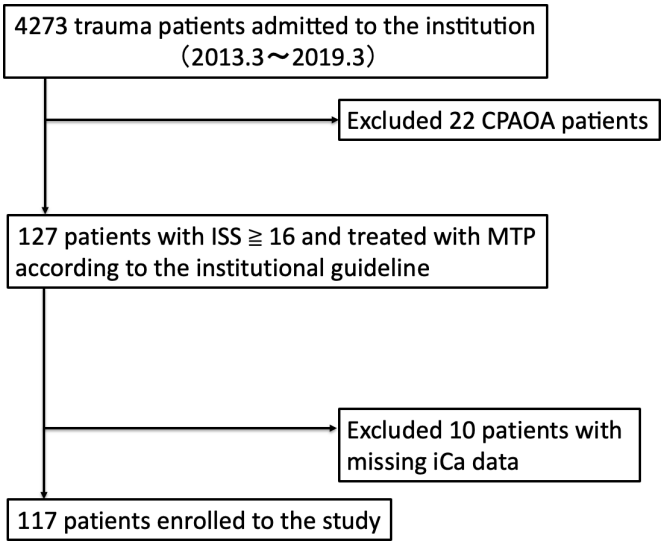

Figure 1 Flow diagram of patient enrollment in the study. CPAOA, cardiopulmonary arrest on arrival; iCa, blood ionized calcium concentration; ISS, Injury Severity Score; MTP, massive transfusion protocol.

underwent operation and/or interventional radiology (IVR) for hemostasis.

Institutional MTP

According to the institutional practice management guidelines for the treatment of severe trauma patients, MTP is triggered when all of the following conditions are met: hemodynamic instability associated with massive bleeding, serum lactate level of 2.5 mmol/L or higher, and expected bleeding volume of 1000 mL or greater. When MTP is triggered, 6 units of unmatched type O red blood cells and 3 g of fibrinogen concentrate are administered pre-emptively. Thereafter, red blood cells (RBC):fresh frozen plasma (FFP):platelet concentrate (PC) is administered in a 1:1:1 ratio.

Data collection

We retrospectively reviewed the medical records of the 117 patients enrolled to collect data on 28-day mortality and patient-specific factors that may influence the mortality. The factors included iCa_ini and iCa_min to represent temporal variations of iCa, age and gender to represent demographic characteristics, and the ISS, initial systolic blood pressure (sBP) and the Glasgow Coma Scale (GCS) score after admission to represent physiological status at admission. The ISS and the Revised Trauma Score (RTS) are indicators of the degree of anatomic and physiologic abnormalities in trauma patients and are routinely used together to predict prognosis. The sBP, GCS score and respiratory rate (RR) are the parameters for calculating the RTS, but we excluded the RR in this study because the data are frequently missing or inaccurate in the patients who underwent endotracheal intubation on arrival, requiring administration of sedatives and muscle relaxants.

We also collected data on treatment-related factors. The factors included doses of blood products (RBC, FFP, and PC) transfused within 24 hours of admission, incidence of calcium supplementation within 24 hours of admission (Ca supplementation), and interventions (operation and/or IVR) applied to control bleeding. Ca supplementations were performed with a single-dose intravenous administration of 2A of calcium gluconate hydrate (total calcium content 7.85 mg/mL or 0.39 mEq/mL).

pH correction of iCa_ini and iCa_min

The iCa_ini and iCa_min were corrected for pH according to simultaneously measured blood pH using the following formula[7 8]:

$$\text{Corrected iCa (mmol/L)} = \text{iCa (mmol/L)} - 0.36 \times (\text{blood pH} - 7.4),$$

where iCa is the blood ionized calcium concentration and pH is simultaneously measured blood pH.

Univariate analyses to evaluate correlation between 28-day mortality and the patient-specific and the treatment-related factors

Univariate analyses were conducted to evaluate correlation between 28-day mortality and the patient-specific or the treatment-related factors. The patients were divided into two groups according to 28-day mortality: the group of the patients who died within 28 days of the injury and the group of those who survived 28 days or longer. Significance of the correlations between the groups and each factor (ie, significance of the differences between the groups) was evaluated using the Mann-Whitney U test for numerical data (iCa_ini, iCa_min, age, sBP, GCS score, ISS, and doses of blood products transfused within 24 hours of admission) and the χ^2 test for categorical data (gender, Ca supplementation, and the interventions). The significance level was set at 0.05.

Multivariate analyses to evaluate correlation between 28-day mortality and temporal variations of ICA

Two multivariate logistic regression models were constructed to evaluate correlation between 28-day mortality and temporal variations of iCa, adjusting for confounding factors. The 28-day mortality was assigned as the dependent variable. iCa_ini or iCa_min, other patient-specific factors that showed a significant correlation with 28-day mortality in univariate analysis, and Ca supplementation were assigned as independent variables.

From a clinical perspective, the doses of blood products transfused within 24 hours of admission were considered as indicators that reflect the effectiveness of MTP and interventions to control coagulopathy and bleeding, rather than factors that affect 28-day mortality. Furthermore, the low doses of blood products transfused within 24 hours of admission may be attributed to early mortality within 24 hours of admission. In the light of these considerations, we did not assign the doses as independent variables in the logistic regression models. On the other hand, since the effect of Ca supplementation on iCa_min and 28-day mortality as a confounding factor cannot be ignored, Ca supplementation was assigned as an independent variable in the logistic regression models.

Quantitative data (iCa_ini, iCa_min, age, and sBP) and qualitative data on ordinal scales (ISS and GCS score) were assigned as continuous variables, and categorical data (28-day mortality, gender, and Ca supplement) were assigned as binomial or dummy variables in the logistic regression models.

ROC analysis to estimate optimal cut-off value to predict 28-day mortality

If multivariate logistic regression demonstrated iCa_ini and/or iCa_min as a significant independent predictor of 28-day

Table 1 Results of the univariate analyses on the association between 28-day mortality and the patient specific factors

28-day mortality	Died within 28 days of injury (n=30)	Survived 28 days or more (n=87)	P value
Factors representing temporal variation in blood ionized calcium concentration			
iCa_ini (mmol/L)	1.07 (0.97–1.12)	1.09 (1.04–1.15)	0.085
iCa_min (mmol/L)	0.80 (0.57–0.93)	0.97 (0.86–1.05)	<0.01*
Factors representing patient characteristics			
Age (years)	68.5 (63.5–78.0)	54.0 (40.0–71.5)	<0.01*
Gender (male:female)	23:07	59:29	0.43
ISS	44.0 (35–54.0)	38.0 (28.0–50.0)	0.027*
Factors representing physiological conditions at admission			
sBP (mm Hg)	59.0 (40.0–74.0)	83.0 (63.0–99.0)	<0.01*
GCS score at admission	3.0 (3.0–7.5)	13.0 (5.5–14.0)	<0.01*

*Provability of equivalence between groups (p value) is smaller than 0.05 or 0.01.
GCS, Glasgow Coma Scale; iCa_ini, initial blood ionized calcium concentration at admission; iCa_min, mnimum blood ionized calcium concentration within 24 hours of admission; ISS, Injury Severity Score; sBP, systolic blood pressure.

mortality, receiver operating characteristic (ROC) analysis was conducted to estimate optimal cut-off value for prediction of 28-day mortality. The optimal cut-off value was estimated applying Youden's index to the ROC curve.[9] Area under curve of the ROC curve was also estimated.

Statistical analysis

All statistical analyses were performed using R V.4.1.0 (The R Foundation for Statistical Computing).[10] The significance level was set at 0.05 two-sided for all tests.

RESULTS

Results of the univariate analysis

Table 1 shows the results of univariate analyses to evaluate the correlation between 28-day mortality and the patient-specific factors including iCa_ini and iCa_min. Low iCa_min (p<0.01), high age (p<0.01), high ISS (p<0.05), low sBP (p<0.01), and low GCS score (p<0.01) were significantly correlated with high 28-day mortality risk.

Table 2 shows the results of univariate analyses to evaluate the correlation between 28-day mortality and the treatment-related factors. High dose of blood products (RBC, FFP, and PC) transfused within 24 hours of admission and incidence of Ca supplementation within 24 hours of admission were significantly associated with high 28-day mortality risk (all p<0.01).

Table 2 Results of the univariate analyses on association between 28-day mortality and the factors related to treatments

28-day mortality	Died within 28 days of injury (n=30)	Survived 28 days or more (n=87)	P value
RBC (units)	24 (16–37)	14 (8–22)	<0.01*
FFP (units)	23 (14.0–35.5)	12 (6.0–23.5)	<0.01*
PC (units)	20 (2.5–27.5)	0 (0–20)	<0.01*
Ca supplementation (Y:N)	18:12	27:60	<0.01*
Operation (Y:N)	19:11	50:37	0.72
IVR (Y:N)	23:07	56:31	0.31

All values except gender and Ca supplementation are expressed as median (IQR).
Ca supplementation denotes incidence of calcium supplementation within 24 hours of admission.
Doses of RBC, FFP or PC were transfused within 24 hours of admission.
*Provability of equivalence between groups (p value) is smaller than 0.05 or 0.01.
FFP, fresh frozen plasma; IVR, interventional radiology; N, no; PC, platelet concentrate; RBC, red blood cell; Y, yes.

Table 3 Multivariate logistic regression model assigning iCa_ini as an independent variable

Independent variable	Adjusted OR (95% CI)	P value
iCa_ini (mmol/L)	0.46 (0.01 to 13.8)	0.65
Age (years)	1.05 (1.02 to 1.08)	<0.01*
ISS	1.02 (0.98 to 1.06)	0.37
sBP (mm Hg) at admission	0.98 (0.96 to 1.00)	0.13
GCS score at admission	0.84 (0.74 to 0.94)	<0.01*
Ca supplementation	2.92 (0.97 to 9.30)	0.06

*Provability of equivalence between groups (p value) is smaller than 0.05 or 0.01.
GCS, Glasgow Coma Scale; iCa_ini, initial blood ionized calcium concentration at admission; iCa_min, minimum blood ionized calcium concentration within 24 hours of admission; ISS, Injury Severity Score; sBP, systolic blood pressure.

Results of the multivariate analyses

Two multivariate logistic regression models were constructed with 28-day mortality assigned as the dependent variable, and iCa_ini or iCa_min and other possible confounding factors assigned as independent variables. The possible confounding factors assigned were age, ISS, sBP, GCS score, and Ca supplementation, which were significantly correlated with 28-day mortality in univariate analyses.

Tables 3 and 4 show adjusted ORs with 95% CIs and p values corresponding to each independent variable in the logistic regression models. In the model with iCa_ini assigned (table 3), high age (p<0.01), low sBP (p<0.05), and low GCS score (p<0.01) were identified as significant independent predictors of 28-day mortality. Whereas, in the model with iCa_min assigned (table 4), low iCa_min (p<0.05), high age (p<0.01), and low GCS score (p<0.01) were identified as significant independent predictors of 28-day death.

Table 5 shows the adjusted ORs and 95% CIs and p values corresponding to each independent variable in the optimized model with iCa_min assigned. Model optimization was performed using a bidirectional stepwise method with the Akaike information criterion (AIC) as the index. AIC was reduced from 100.5 to 98.9 by the optimization. In the optimized model, low iCa_min (p<0.01), high age (p<0.01), and low GCS score (p<0.01) were identified as significant independent predictors of 28-day mortality.

Table 4 Multivariate logistic regression model assigning iCa_min as an independent variable

Independent variable	Adjusted OR(95% CI)	P value
iCa_min (mmol/L)	0.05 (0.01 to 0.71)	0.03*
Age (years)	1.05 (1.02 to 1.09)	<0.01*
ISS	1.02 (0.98 to 1.07)	0.31
sBP (mm Hg) at admission	0.99 (0.97 to 1.01)	0.27
GCS score at admission	0.84 (0.74 to 0.95)	<0.01*
Ca supplementation	1.92 (0.55 to 6.66)	0.3

*Provability of equivalence between groups (p value) is smaller than 0.05 or 0.01.
GCS, Glasgow Coma Scale; iCa_ini, initial blood ionized calcium concentration at admission; iCa_min, minimum blood ionized calcium concentration within 24 hours of admission; ISS, Injury Severity Score; sBP, systolic blood pressure.

Table 5 Optimized multivariate logistic regression model assigning iCa_min as an independent variable

Independent variable	Adjusted OR (95% CI)	P value
iCa_min (mmol/L)	0.03 (0.002 to 0.4)	<0.01*
Age (years)	1.05 (1.02 to 1.09)	<0.01*
sBP (mm Hg) at admission	0.98 (0.96 to 1)	0.13
GCS score at admission	0.84 (0.74 to 0.94)	<0.01*

*Provability of equivalence between groups (p value) is smaller than 0.05 or 0.01.
GCS, Glasgow Coma Scale; iCa_ini, initial blood ionized calcium concentration at admission; iCa_min, minimum blood ionized calcium concentration within 24 hours of admission; ISS, Injury Severity Score; sBP, systolic blood pressure.

Results of the ROC analysis

Figure 2 shows the ROC curve for evaluating accuracy of predicting 28-day mortality from iCa_min and estimation of the optimal cut-off values with application of Youden's index. The estimated optimal cut-off values for iCa_min to predict 28-day mortality was 0.95 (95% CI 0.63 to 0.84) mmol/L with the sensitivity and specificity of 0.59 and 0.83, respectively. The area under the curve (AUC) of the ROC curve was 0.73 (95% CI 0.63 to 0.84), which indicates 'fair' ($0.7 \leq AUC < 0.8$) accuracy of the prediction.[11]

DISCUSSION

In this study, we investigated the relationship between short-term prognosis and the first measured iCa value after admission (iCa_ini) and the minimum iCa value within 24 hours after admission (iCa_min) as indices of temporal variations of blood iCa for patients with traumatic hemorrhagic shock who had undergone an MTP and operation and/or IVR for hemostasis. The logistic regression analysis revealed that low iCa_min was a significant independent predictor of 28-day mortality. Furthermore, ROC analysis revealed that the cut-off value for iCa_min to predict 28-day mortality was 0.95 mmol/L.

Several studies have reported correlations between hypocalcemia at admission (low iCa_ini) and the need for massive blood transfusions or poor short-term prognosis.[3–6] On the other hand, a study found no significant correlation between iCa_ini and in-hospital mortality.[12] The only thing these reports have in common is their emphasis on the importance of iCa in the resuscitation of severe trauma patients.

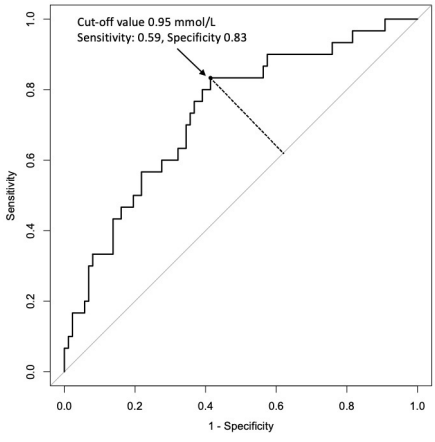

Figure 2 Receiver operating characteristic curve for evaluating accuracy of predicting 28-day mortality from minimum blood ionized calcium concentration within 24 hours of admission and estimation of the optimal cut-off values with application of Youden's index.

In this study, there was no significant correlation between iCa_ini and 28-day mortality in either univariate or multivariate analysis. This result may be attributed to the correction of iCa within 24 hours of admission by Ca supplementation, which was performed in almost 40% (45 of 117 patients) of enrolled patients. Ca supplementation for the patients with low iCa_ini may have contributed to the increase in iCa_min and to the survival of some patients as well. Therefore, Ca supplementation was assigned as an independent variable in the logistic regression model to account for the possibility that it is a confounding factor affecting both iCa_min and 28-day mortality.

This study appears to be the first to correlate iCa_min with short-term prognosis in trauma patients with massive bleeding. Furthermore, iCa_ini, like age and ISS, is already determined at the time of admission and is not a meaningful indicator of interventions to improve outcomes. However, in terms of iCa_min, establishment of an MTP oriented toward avoiding severe hypocalcemia (iCa-directed MTP) may improve outcomes,[13] and calcium supplementation to maintain iCa above the cut-off values identified in this study may thus improve short-term outcomes. The present results are thus expected to contribute to the establishment of iCa-directed MTP and, ultimately, to improved outcomes for patients with traumatic hemorrhagic shock. Conversely, overcorrection of iCa has been reported to increase the risk of mortality.[14 15] An iCa-directed protocol thus needs to be established by setting an upper target limit for iCa in addition to the lower target limit identified in the present study and by standardizing the timing of iCa monitoring.

Several mechanisms are involved in the interaction of hypocalcemia in severe hemorrhagic trauma with the triad of traumatic death (hypothermia, coagulopathy, and acidosis). Hypothermia has been reported to reduce in vivo metabolic function, resulting in citrate accumulation, which chelates calcium and contributes to hypocalcemia.[16]

Decreased myocardial contractility associated with hypocalcemia has also been reported to prolong shock and cause acidosis.[1] Further, calcium is an essential coagulation factor for blood clot formation,[17–19] and hypocalcemia has been reported to cause coagulopathy.

Among several mechanisms by which such hypocalcemia affects the short-term prognosis of patients with traumatic hemorrhagic shock, the present study focused on the relationships to coagulopathy. iCa is also known to be affected by blood pH, and it has been reported that a decrease in blood pH can exacerbate coagulation disorders by slowing clot formation.[18–20] Therefore, we used iCa values corrected by pH in the present study to avoid blood pH as a confounding factor when examining the impact of hypocalcemia on short-term prognosis of the patients with traumatic hemorrhagic shock. On the other hand, since ionized calcium in the blood is buffered by lactic acid, calcium supplementation based on pH-corrected iCa may risk overcorrection in the presence of lactic acidosis. Therefore, a similar study was conducted using iCa_min values without pH correction, which identified the cut-off value as 1.01 mmol/L (AUC 0.718), approximately 10% higher than that with pH correction. This difference of 10% in iCa with and without pH correction is consistent with the previous studies.[7 21] When considering calcium supplementation based on iCa monitoring in practice, this relationship between correction by blood pH and lactic acidosis should be considered.

There are several limitations to this study that should be considered. The first limitation stems from the relatively low 28-day mortality rate among the enrolled patients (30 out of 127). Consequently, events per variable (EPVs) of the logistic

regression models was 6 (30 events for five independent variables), which is relatively small to warrant stability of the model. Controversy is ongoing regarding the minimum EPV required for a stable logistic regression model, with several simulation-based studies reporting diverse results.[22–24] Furthermore, another simulation-based study emphasized the importance of total sample size over EPV,[25] and the relatively large sample size of 127 patients enrolled in the present study may favor the stability of the logistic regression models. Nevertheless, further investigation enrolling an increased number of the patients is warranted to construct stable logistic regression models and to draw scientifically rigorous conclusions.

The second limitation stems from the relatively long patient enrollment period of 6 years. Although the criteria for triggering MTP have not been revised during the period, indications for operation and IVR may have changed, and the techniques and outcomes of these interventions may have improved. However, the impact of such changes and improvements on 28-day mortality was not considered in the present study and warrants further investigation.

CONCLUSION

In the management of the trauma patients with massive hemorrhage, aggressive correction of iCas to maintain 0.95 mmol/L or higher within 24 hours of the admission is expected to improve their short-term outcomes.

Contributors TI and MS (1) made substantial contributions to the study concept or the data analysis or interpretation, (2) drafted the article or revised it critically for important intellectual content, (3) approved the final version of the article to be published and (4) agreed to be accountable for all aspects of the work.TI is responsible for the overall content as guarantor.

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