Title

Lower Serum Calcium Level Is Associated With Hemorrhagic Transformation After Thrombolysis

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Lower serum calcium level is associated with hemorrhagic transformation after thrombolysis

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Abstract

Background and Purpose—We aim to investigate whether lower admission serum calcium levels are associated with hemorrhagic transformation (HT) after intravenous thrombolysis (IVT).

Methods—A total of 362 patients treated with IVT was divided into four quartiles based on admission serum calcium levels (Q1[<2.16], Q2[2.16, 2.23], Q3[2.24, 2.31], Q4[>2.31] mmol/L). HT was classified as hemorrhagic infarction (HI) and parenchymal hemorrhage (PH). Logistic regression was applied to assess the association between serum calcium levels and the incidence of HT.

Results—Compared with Q4, HT was more common in Q1 (OR=2.580, 95% CI: [1.258, 5.292], p=0.010), Q2 (OR=2.382, 95% CI: [1.163, 4.877], p=0.018) and Q3 (OR=2.293, 95% CI: [1.133, 4.637], p=0.021). HI was more common in Q1 (p=0.037), and Q2 (p=0.018), compared with Q4, and PH was more common in Q1 (p=0.029) than Q4.

Conclusions—Lower admission serum calcium level is independently associated with HT after IVT, and this hypothesis needs larger confirmatory trials.

Keywords

serum calcium; stroke; thrombolytic therapy; hemorrhagic transformation

Introduction

Hemorrhagic transformation (HT) is the main complication of intravenous thrombolysis (IVT) after ischemic stroke.[1-3] Previous studies have demonstrated that low serum calcium level is associated with poor outcome, extensive infarction in ischemic stroke patients, and

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Disclosure

Dr Liebeskind: 1) Consultant/advisory board (modest)-Stryker and Covidien; 2) University of California (UC), which holds a patent on retriever devices for stroke, at the time of this work.

large hematoma volumes in intracerebral hemorrhage patients.[4-7] As an essential cofactor in the coagulation cascade, calcium ion plays an important role in the conversion of prothrombin to thrombin. The association of decreased calcium levels with prolonged clotting time and bleeding tendency has been shown in rodent models.[8] We therefore hypothesized that patients with lower serum calcium levels may be more likely to experience HT after IVT.

Subjects and Methods

Consecutive patients admitted to our department from March 2010 to August 2014 were prospectively considered. The inclusion criteria for enrollment were 1) age 18 years or older; 2) diagnosis of acute ischemic stroke and treatment with IV rt-PA within 6 hours of symptom onset; 3) serum calcium level collected on admission; 4) CT/MRI performed 24 hours after IVT. Patients were excluded if endovascular interventions were performed. IV rt-PA (Alteplase 0.9 mg/kg up to a maximum of 90 mg) was used with 10% of the total dosage as a bolus and the rest over 1 hour.

We used DWI lesion volume on MRI or the volume of the brain tissue with a relative CBF <30% on perfusion CT together as the volume of the infarct core.[9] We divided HT within 24h after thrombolysis into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) on the basis of imaging characteristics, referring to ECASS II definition.[10]

Fisher's exact test was used to compare the dichotomous variables between groups, while t-test, or Mann-Whitney U test was used for the continuous variables. One-way ANOVA or Kruskal-Wallis test was used between multiple groups. For multivariate analysis, the pool of covariates were determined based on univariate analysis at $p<0.1$ level and previous literature. All statistical analysis was performed by SPSS 19.0.

Results

A total of 362 patients met study criteria, HT was evaluated on MRI (n=259) and CT scan (n=103) within 24 hours after IVT, affecting 115(31.8%) patients, among whom 80(22.1%) had HI and 35(9.7%) had PH. Incidence of HT in each calcium quartile was 40.2% in Q1, 33.0% in Q2, 33.3% in Q3 and 21.5% in Q4, respectively. Incidence of HI in each calcium quartile was 25.6% in Q1, 26.6% in Q2, 22.6% in Q3 and 14.0% in Q4, respectively. Incidence of PH in each calcium quartile was 14.6% in Q1, 6.4% in Q2, 10.8% in Q3 and 7.5% in Q4, respectively.

Supplemental Table I (please see http://stroke.ahajournals.org) gives the demographic characteristics and clinical variables by calcium quartiles. Logistic regression found that compared with Q4, the incidence of HT was significantly higher in Q1, Q2 and Q3, as shown in Table 1. HI is more common in Q1, and Q2, compared with Q4. Q3 has a tendency to have more HI than Q4, but failed to reach a statistical significance. Q1 was more likely to have PH than Q4, while Q2 and Q3 did not reach statistical significance (Table 1). The results were similar when infarct volume was included in the logistic regression model (Supplemental Table II, please see http://stroke.ahajournals.org).

Discussion

To our knowledge, this is the first study investigating the relationship between admission serum calcium level and HT after IVT. We found that a lower admission serum calcium level was associated with a higher incidence of HT within 24 hours after IVT.

In previous studies, a lower admission serum calcium level within 24 hours after ischemic stroke onset is associated with higher baseline NIHSS score, larger infarct volume, and poor discharge functional outcome.[4,5] In our study, we found that lower admission serum calcium level was associated with HT after IVT. Micozkadioglu et al found a slight elevation in admission serum calcium level in 27 HT patients out of 160 stroke patients.[11] However, multivariate analysis was not performed and the percentage of patients treated with IVT was not mentioned. In patients with acute intracerebral hemorrhage, admission serum calcium level was also found to be negatively related to hematoma volume.[6]

There are two possible mechanisms which may explain the association between serum calcium level and HT after IVT. First, calcium ion is an essential cofactor in the coagulation cascade and plays an important role in the conversion of prothrombin to thrombin. In rodent models, decreased calcium levels was found to be associated with prolonged clotting time and bleeding tendency.[8] Second, evidence demonstrated that the activation of extracellular calcium receptors located in the perivascular sensory nerves could lead to the release of vasodilator substance, which mediated the relaxation of isolated arteries.[12] Therefore, due to the decreased Ca^{2+}-induced relaxation of isolated arteries, lower serum calcium level may result in the persistent constriction of the blood vessels in the peri-ischemic zone, which subsequently elevates local blood pressure and causes HT.[6]

Our study has limitations. First, it is limited by the single-center, hospital-based, retrospective design. Second, our study only focused on total serum calcium, while ionized calcium, the physiologically active compartment, was not measured. Third, a progressive decrease along the 1 to 4 quartiles was followed in the proportion of HI, but not in the PH quartiles. This nonproportional effect could be due to the relatively low incidence of PH. Studies based on larger population is thus needed.

In conclusion, lower admission serum calcium level is independently associated with HT in 24 hours after thrombolysis. Admission serum calcium level might be used as one of the predictors for HT after thrombolysis. Further investigations will be needed to test this hypothesis and then elucidate the potential neuroprotective mechanism of serum calcium.

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Table 1

Multivariate Analysis for Hemorrhagic Transformation

	OR	P value
HT*		
Q1	2.580 (1.258 to 5.292)	0.010
Q2	2.382 (1.163 to 4.877)	0.018
Q3	2.293 (1.133 to 4.637)	0.021
Q4	Ref	-
HI†		
Q1	2.365 (1.055 to 5.302)	0.037
Q2	2.571 (1.174 to 5.632)	0.018
Q3	2.153 (0.973 to 4.762)	0.058
Q4	Ref	-
PH†		
Q1	3.536 (1.135 to 11.022)	0.029
Q2	1.949 (0.543 to 7.001)	0.306
Q3	3.068 (0.956 to 9.842)	0.059
Q4	Ref	-

*Adjusted by age, baseline NIHSS score, atrial fibrillation, serum glucose, smoke, and platelet count.

†Adjusted by age, baseline NIHSS score, atrial fibrillation, and serum glucose.