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The correlation between blood calcium level, hematoma volume, stroke severity and prognosis in patients with acute cerebral hemorrhage

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Abstract. – OBJECTIVE: The objective of the present study was to determine the correlation between blood calcium level, hematoma volume and stroke severity in the prognosis of acute cerebral hemorrhage patients.

PATIENTS AND METHODS: We selected 125 patients with acute cerebral hemorrhage admitted within 24 hours of symptom onset. Blood calcium levels were assessed by standard biochemical methods. Hematoma volume was measured by quantitative computed tomography. NIHSS (National Institutes of Health Stroke Scale) scores at one month, and the differences in survival rate and survival period at follow-up visits were assessed.

RESULTS: Hematoma volume and NIHSS scores of the hypocalcemic group were higher than those of the hypercalcemic group. Those of the normocalcemic group were the lowest, and the differences were statistically significant ($p < 0.05$). The survival rate and survival period of the normocalcemic group were higher than those of the other two groups and the differences were statistically significant ($p < 0.05$). The logistics regression analysis showed that the APACHE II score, blood calcium level upon admission and hematoma volume were independent risk factors for survival ($p < 0.05$).

CONCLUSIONS: If blood calcium level is too low or too high, hematoma volume and stroke severity of acute cerebral hemorrhage patients may increase and is related to long-term survival.

Key Words:
Blood calcium, Acute cerebral hemorrhage, Hematoma volume, NIHSS, Survival rate.

Introduction

Acute cerebral hemorrhage (ACH) is a common cerebrovascular disease and hematoma volume is closely related to the prognosis[1,2]. It has been previously shown[3] that blood calcium level upon hospital admission is related to hematoma volume, stroke severity and prognosis. Low blood calcium (hypocalcemia) often leads to increased hematoma volume and poor prognosis. Additionally, blood calcium is closely related to the occurrence of ischemic stroke. Between 1988 and 1990, Iso et al4[3] followed the diets of 110792 Japanese volunteers, aged 40 to 79, who had no history of stroke, coronary heart disease or cancer. Among them, 273 died of an ischemic stroke. After adjusting for risk factors such as age, smoking and other parameters, the calcium content in the diet significantly and negatively correlated with the appearance of ischemic stroke. The comparison between males with the highest and lowest calcium acceptable daily intake (ADI) showed that the relative risk of ischemic stroke was 0.53 (95% CI: 0.29-0.99). The relative risk in females was 0.50 (95% CI: 0.27-0.95). Therefore, some authors recommend that increasing the calcium intake in the diet is preventative for stroke[5]. However, other studies showed that increases of blood calcium could promote the occurrence of stroke. Bolland et al[6] carried out randomized controlled trials on the occurrence of cardiovascular and cerebrovascular events among healthy female seniors who took calcium supplements. The results showed that the relative risk of stroke was 1.37 (95% CI: 0.83-2.28). The morbidity ratio between the control group and the placebo group was 1.45 (95% CI: 0.88-2.49). The total amount of calcium (diet and supplement) in this study was roughly 2400 mg/d, which was higher than the maximum daily dose of calcium needed. Therefore, there might be discrepancies in the results. A 2010 meta-analysis[7] included 15 experiments, 8151 subjects and an average follow-up visit period of 3.6 years. The group with calcium supplement intake ≥ 500 mg/d were taken as the experimental group, while the rest were the con-

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trol group. The results showed no significant increase in the occurrence rate of stroke: 1.20 (95% CI: 0.96-1.50, $p = 0.11$).

There is no definite opinion on the correlation between blood calcium and occurrence of stroke and the specific mechanism as to how blood calcium affects the occurrence of stroke remains unknown. Based on these facts, the aim of the present study was to determine the correlation between blood calcium level, hematoma volume, stroke severity and prognosis of patients with acute cerebral hemorrhage in order to provide guidance and reference for diagnosis and treatment.

Patients and Methods

Patients

We selected 125 patients who had acute cerebral hemorrhage for the first time (disease time within 24 hours) in our hospital from January 2010 to June 2015. The exclusion criteria included: traumatic cerebral hemorrhage, cerebral hernia, critical state such that expected survival did not exceed one month, coagulation disorders, and recent intake of antiplatelet drugs. We obtained informed consent from patients and their families and approval from the Ethics Committee of our hospital for the study. Standard medical procedures were applied for treatment. The study included 72 males and 53 females. They were aged from 42 to 76 years old, with an average age of 62.5 ± 14.2 years. The time of cerebral hemorrhage was from one to 22 hours, with an average of 10.5 ± 4.6 hours. The average systolic pressure was 153-204 mmHg, with an average of 172.6 ± 22.7 mmHg. The average diastolic pressure was 72-112 mmHg, with an average of 92.4 ± 16.8 mmHg. The APACHE II score was 42-63, with an average of 52.8 ± 10.6. Based on the blood calcium level, 35 cases were categorized as the hypocalcemic group (< 2.25 mmol/l), 75 cases as the normocalcemic (normal blood calcium) group (2.25-2.75 mmol/l), and 15 cases as the hypercalcemic (high blood calcium) group (≥ 2.75 mmol/L). The baseline information of the three groups was comparable.

Research Methods

Standard biochemical methods were applied to test the blood calcium levels upon admission. The NIHSS score[8] after one month and survival rate after one year were determined. A Lightspeed 16-row spiral CT (GE, Fairfield, CT, USA) was used to measure hematoma volume (before treatment). The scanning parameters were: layer thickness = 10 mm, voltage = 120 KV, and current = 250 mA. The scope of the hematoma was confirmed by supporting hematoma measurement software which allowed for pseudocoloring. We applied the automatic measurement to obtain the values for the hematoma volume. NIHSS score includes consciousness (0-3 points), gaze (0-2 points), view (0-3 points), facial paralysis (0-3 points), upper limbs movement (0-4 points), lower limb movement (0-4 points), ataxia (0-2 points), feeling (0-2 points), language (0-3 points), dysarthria (0-2 points) and negligence (0-2 points). Higher scores indicated more severe symptoms.

Statistical Analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The measurement data are presented as mean ± standard deviation. We applied single factor ANOVA analysis for comparison among groups. Fisher's LSD test was used for pairwise comparisons. Enumeration data are presented as number of cases (%). Corrected χ^2 test was used for comparisons among groups. Logistics model was used for multi-factor regression analysis. The follow-up visits ended in January 2016. The Kaplan-Meier model and Long-rank χ^2 test were used for survival time. $p < 0.05$ was taken as statistically significant.

Results

Comparison of Hematoma Volume and NIHSS Score

Hematoma volume and NIHSS scores of the hypocalcemic group were higher than in the hypercalcemic group. Hematoma volume and NIHSS scores of the normocalcemic group were the lowest. The differences between groups were statistically significant ($p < 0.05$) (Table I).

Table I. Comparison of hematoma volume and NIHSS score.

Group	Hematoma volume (ml)	NIHSS score
Hypocalcemia	15.6 ± 4.3	92.6 ± 21.5
Nornocalcemia	7.2 ± 3.0	53.4 ± 23.4
Hypercalcemia	10.5 ± 3.6	72.0 ± 26.7
F	8.624	9.203
p	0.010	0.005

Comparison of Survival Rate

The follow-up visit period for the three groups was 35 months. There were 14 deaths due to cerebrovascular events in the hypocalcemic group (40.0%), eight deaths in the normocalcemic group (10.7%), and six deaths in the hypercalcemic group (40.0%). The comparison of the survival rates of the three groups showed statistically significant differences ($\chi^2 = 14.757$, $p = 0.001$). The survival period of the normocalcemic group was higher those of the other two groups and the differences were statistically significant ($\chi^2 = 12.243$, $p = 0.002$) (Figure 1).

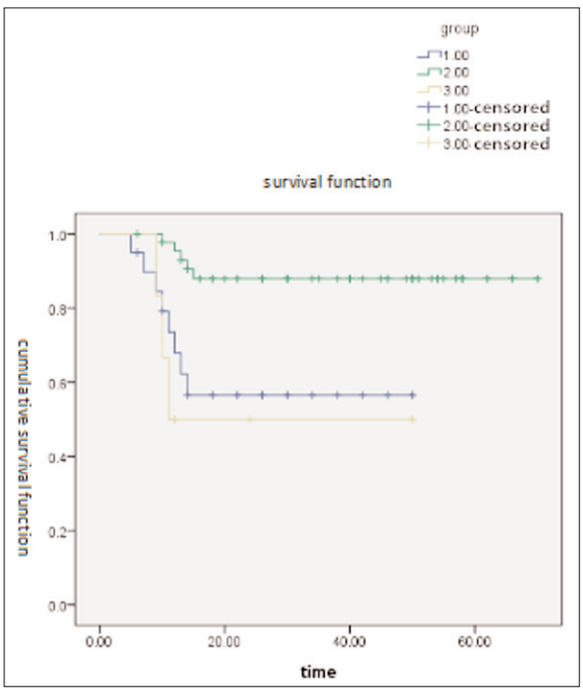

Figure 1. Comparison of the Survival Period among groups with different levels of blood calcium. (1 = hypocalcemic group; 2 = normocalcemic group; 3 = hypercalcemic group).

Multi-factor Regression Analysis

Gender, age, disease time, average systolic and diastolic pressure, APACHE II score, blood calcium level upon admission, hematoma volume and NIHSS score were regarded as independent variables. Patient survival was the dependent variable. According to this model, we arrived at the conclusions that the APACHE II score, blood calcium level upon admission and hematoma volume were the independent risk factors for survival ($p < 0.05$) (Table II).

Discussion

Inoue et al[9] studied the factors affecting the prognosis of a cerebral hemorrhage. Their results showed that when patients with acute cerebral hemorrhage were admitted to the hospital, low blood calcium predisposed to large volume cerebral hematomas. The 273 patients with acute cerebral hemorrhage within 24 h of symptom onset were divided into four different groups based on blood calcium levels upon admission (Q1 [≤ 9.0], Q2 [9.1-9.3], Q3 [9.4-9.7] and Q4 [≥ 9.8] mg/dl). The average hematoma volume among Q1 to Q4 were 18, 9, 10 and 9 ml, respectively ($p = 0.005$), and the average NIHSS scores were 16, 11, 11, and 9, respectively ($p = 0.010$). The multi-factor analysis showed that the average hematoma volume of Q1 patients ($p = 0.025$) was relatively higher than that of the Q4 patients, and the NIHSS scores of the Q1 patients were relatively higher than those of Q4 patients. The modified Rankin scale showed that, after adjusting for risk factors and other complications, the number of patients with 0-2 points in Q1 was smaller than that of Q4 (dominance ratio 0.31, 95% credibility interval is 0.11-0.84). The comparison lost significance after adjusting the hematoma volume and NIHSS scores. The original data showed that compared with Q4, the number of patients with the modified Rankin scores between five and six and poorer prognosis were higher in Q1. However, there was no significance after adjustment.

The mechanisms whereby blood calcium reduces the occurrence of stroke include:

Table II. Multi-factor regression analysis.

Model	β	Wald	p	OR	95% CI
APACHE II score	0.102	4.627	0.033	1.627	0.217-3.231
Blood calcium level upon admission	0.232	5.326	0.018	1.865	1.121-3.627
Hematoma volume	0.156	6.457	0.012	2.231	2.021-3.564

1. Improvement of lipid metabolism and control of obesity[10]. Within the intestinal canal, calcium can reduce the absorption and levels of fat in blood by integrating with fatty acids. High intake of calcium can lower the levels of vitamin A, and further accelerate lipolysis and inhibit fat synthesis. High calcium intake can inhibit the secretion of hypothalamic neuropeptides, and lead to loss of appetite, so that lipid synthesis is restricted, and serum cholesterol and triglyceride are lowered. High calcium intake increases the level of free triiodothyronine in serum and increases basal body metabolism. The energy consumption will be increased to inhibit obesity.
2. Lowering of blood pressure[11]. Calcium supplements can lower the risk of high blood pressure by 20-25%. The intake of calcium can increase the content and activity of nitric oxide (NO) synthase. Increased NO content leads to activation of soluble guanylyl cyclase. The calcium influx in cells will be reduced, thus inhibiting combination of myoglobin and myosin. As a result, vascular smooth muscle will be relaxed and blood pressure will be lowered. Calcium intake can increase the activity of calcium and sodium pumps to reduce the membrane permeability and stabilize membranes. In addition, calcium intake can attenuate the inhibitory effect of high sodium on sodium pumps, reduce calcium influx in vascular smooth muscle cells, relax the smooth muscle and lower blood pressure. Calcium intake can regulate the expression of parathyroid hypertensive factor and calcitonin gene-related peptide, which are both vasoactive substances. Calcium can alter the level of noradrenaline release from the hypothalamus. It can also specifically adjust the activity of 1-adrenergic receptors in peripheral tissues. Through the comprehensive function of the central and peripheral nervous system, blood pressure can be adjusted. The intake of calcium can enhance natriuresis, and lower blood volume to lower the pressure.
3. Stabilize blood glucose[12]. A follow-up study from the US found that patients with high calcium intake had a 21% lower risk of having diabetes compared with those with low calcium. Calcium can function as a "switch" for insulin release. When blood calcium levels reach certain concentrations, pancreatic β-cells are stimulated to secrete insulin and increase the sensitivity of the body to insulin so that hyperinsulinemia in inhibited and glucose level can be lowered.

A previous study[13] on blood calcium level and mortality within one year from cerebral stroke indicated that both hypo- and hypercalcemia are associated with increased rate of mortality among patients with stroke. The correlation is non-linear. For acute stroke patients with diabetes and hypertension, increased mortality rate due to hypercalcemia may be related to accelerated atherosclerosis, angiosteosis, plaque rupture, and other risk factors related to metabolism. A meta-analysis of a prospective study[14] on the correlation between calcium and risk of stroke (including 371495 participants and 10408 incidences of stroke) showed that the correlation between calcium intake and stroke was non-linear. The correlation between calcium intake and both ischemic stroke and hemorrhagic stroke showed no significant differences. High or low intake of calcium did not have obvious protective effects on ischemic stroke. The calcium intake from dairy products can lower the risk of stroke by about 24% (RR = 0.76, 95% CI: 0.66-0.86). In addition, calcium supplementation did not correlate with risk of stroke. Long-term follow-up visits found that calcium is a protective factor for stroke.

Conclusions

From the present study, hematoma volume and NIHSS scores of the hypocalcemic group were significantly higher than those of the hypercalcemic group. These parameters were lowest in the normocalcemic group and the differences were statistically significant. The survival rate and survival period of the normocalcemic group were significantly higher than those of the other two groups. The logistics regression analysis result showed that the APACHE II score, blood calcium level upon admission and hematoma volume were independent risk factors for survival. If the blood calcium level is too low or too high, hematoma volume and stroke severity of acute cerebral hemorrhage patients may be increased, which is related to long-term survival.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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