Studying the role of serum calcium as a prognostic factor of acuteischemic stroke

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Abstract: Background: Although the relationship of serum calcium (Ca^{2+}) levels and the pathways involved in cell death in acute cerebral ischemia remains unclear; clinical studies suggest that serum Ca^{2+} levels may be associated with severity of clinical symptoms, prognosis and infarct volume. The decrease in serum Ca^{2+} may reflect a response to the presence of tissue ischemia. **Objectives:** Evaluation of the prognostic significance of the levels of serum Ca^{2+} that obtained from the patient within 6 hours and at 72-96 hours of the onset of ischemic stroke. **Patients and methods:** The study consisted of 50 acute ischemic stroke patients older than 18 years, who were admitted to the hospital within 6 hours of stroke onset. All patients were subjected to the following: detailed history taking, thorough general and neurological examination, Laboratory investigations, brain CT scan, brain MRI including DWI, Carotid duplex and Echocardiography. Serum calcium (total and ionized) was obtained from the patients on admission and 72-96 hours post event. **Results:** There was no difference between admission total Ca^{2+} quartiles regarding age distribution, sex distribution, risk factors and laboratory investigations. All cases showed a decline in both total and ionized calcium. Serum Ca^{2+} obtained after 72-96 hours post event showed a significant decrease in comparison to serum calcium obtained within 6 hours from stroke onset. Early serum Ca^{2+} had no prognostic significance, there was weak or no correlations between the admission total calcium from side and the stroke severity, global disability, functional independency and infarct size from the other side. Late serum calcium (obtained from the patient 72-96 hours post event) is of prognostic significance. The level of late serum Ca^{2+} is inversely proportional to the stroke severity, stroke disability and MRI infarct size, while it was directly proportional independency. **Conclusion:** In ischemic stroke patients, the early serum calcium is apparently within the normal ranges. During the first 3 days of ischemic insult, serum calcium (total/ionized) is at least temporarily decreased. This decrease reflects a response to tissue ischemia. The extend of this decrease is directly proportional to the stroke severity, the size of brain infarcts and the degree of disability.

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1. Introduction

Stroke is the most frequent cause of adult disability and the third cause of reduced quality of life, after depression and heart attack, in the elderly. Ischemic stroke accounts for about 75% of all stroke cases **(Cherubini *et al.*,2005 and Divani, 2011).**

Calcium (Ca^{2+}) plays an important role in the pathogenesis of ischemic cell damage. The neuro-chemical consequences of ischemia include excessive release of neurotransmitters, particularly glutamate, excessive activation of post synaptic glutamate receptors, excessive sodium and calcium ion entry to cells. Intracellular Ca^{2+}accumulation leads to neuronal damage by triggering the cycle of cytotoxic events that include activation of calcium dependent intracellular enzyme system, that lead to free radical production, membrane lipid breakdown and proteolysis **(Muir, 2002 and Guven *et al.*,2011).**

Many clinical studies suggest that serum Ca^{2+} levels may be decreased after cerebral ischemia and this decrease is associated with severity of clinical symptoms, prognosis and infarct volume**(Ovbiagele *et al.*,2006; Buck *et al.*,2007 and Ovbiagele *et al.*,2008).**

Cerebral ischemia causes at least temporary depletion of extracellular Ca^{2+} because of Ca^{2+}influx and intracellular Ca^{2+}accumulation. But it is not clear whether the magnitude and temporal course of this disease is sufficient to account for the lower Ca^{2+} levels observed in patients with infarction **(Guven *et al.*, 2011).**

2. Methods

The present study was a prospective study which was conducted in the neurology department of Al-Azhar University Hospital in Damietta in the period from January 2013 to September 2013. It included 50 acute ischemic stroke patients older than 18 years, who were admitted to the hospital within the first 6 hours of stroke onset. Patients with cerebral venous sinus thrombosis were excluded. Patients with pre-existing

congestive heart failure or severe metabolic illness that could alter serum electrolytes were excluded. The included patients were presented by acute onset of focal neurological deficit confirmed by presence of recent brain infarction in diffusion weighted MRI. The severity of ischemic stroke was assessed on admission and after 72 hours by means of the National Institutes of Health Stroke Scale (NIHSS). The degree of disability and the functional independency were assessed after 3 months by means of the Modified Rankin Scale (MRS) and the Barthel Index (BI) respectively. Serum calcium was obtained from the patients on admission and 72 hours after the onset of ischemic stroke.

Statistical Analysis

The data were organized, tabulated and analyzed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21. The values of serum calcium of the studied sample were expressed as mean and standard deviation (SD). For comparison between the mean admission serum calcium and the mean 72 hours serum calcium, the Student paired t test was used. The bivariate correlation between the values of serum calcium and the different prognostic tools (NIHSS, MRS and BI) as well as the MRI-infarct size was done by means of Pearson's coefficient correlation. For interpretation of results; p value < 0.05 was considered significant while p value < 0.001 was considered extremely significant.

3. Results

A total of 50 patients above the age of 18 years with acute ischemic stroke including 25 men and 25 women were enrolled in the study. The mean admission serum calcium of the studied sample was (total calcium 9.72±0.47 mg/dL and ionized calcium 1.28±0.08 mmol/L) while the mean 72 hours serum calcium was (total calcium 8.90±0.82 mg/ dL and ionized calcium 1.18±0.09 mmol/L) and according to unpaired *t*test there was extremely significant decrease in the levels of 72 hours serum calcium when compared to their levels on admission(p< 0.001) **Figures (1, 2).** By using the bivariate correlation, It was shown that the admission total calcium was weakly correlated to baseline NIHSS (r = - 0.011, p =0.940); 72 hours NIHSS (r =-0.005, p = 0.974);

Δ NIHSS (r = - 0.005, p = 0.974); 3 months MRS (r = -0.026, p =0.859); and 3 months BI (r = 0.028, p = 0.877). These mean that serum calcium obtained very early from the patients showed no prognostic significance. On the other side the levels of 72 hours total calcium were of prognostic significance. The 72 hours total calcium was strongly correlated to baseline NIHSS (r = - *759*, P< 0.001); and 72 hours Δ NIHSS (r = - 0.784, p < 0.001); reasonably correlated to ΔNIHSS(r =0.478, p < 0.001); strongly correlated to 3 months MRS (r = -0.775, p <0.001) and 3 months BI (r = 0.780, p <0.001). This means that the level of 72 hours total calcium is inversely proportional to the baseline and the 72 hours stroke severity and the 3 months global disability and is directly proportional to the clinical neurological improvement and the 3 months functional independency. It was also shown that the decline in total calcium during the first 72 hours of stroke is strongly correlated to baseline NIHSS (r = 0.840, p <0.001); 72 hours NIHSS (r =-0.900, p < 0.001); 3 months MRS (r = 867, p<0.001) and 3 months BI (r = -0.874, p<0.001) and reasonably correlated to Δ NIHSS (r =-0.572, p <0.001). This means that the decline in total calcium during the first 72 hours of stroke is directly proportional to the baseline and the 72 hours stroke severity, the 3 months global disability and is inversely proportional to the clinical neurological improvement and the 3 months functional independency **(Figure 3, 4, 5).**

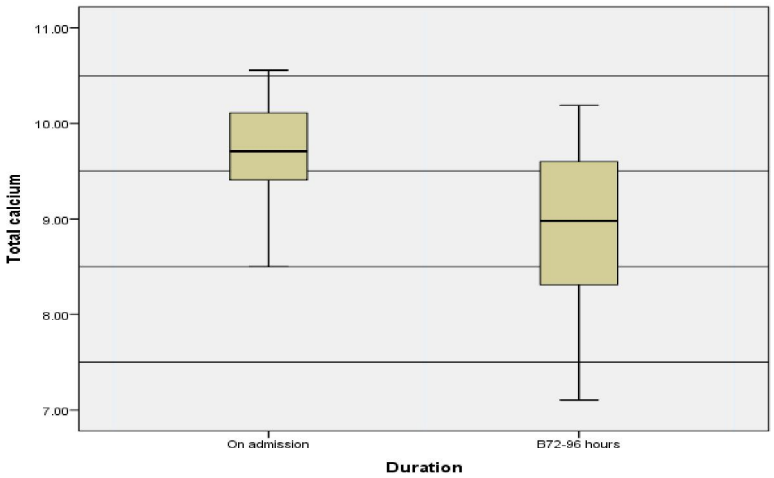

Figure (1): Comparison between serum total calcium (mg/dL) on admission and after 72-96 hours from stroke onset.

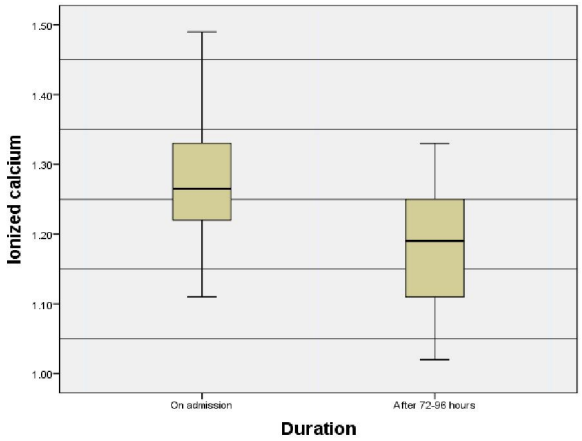

Figure (2): Comparison between serum ionized calcium (mg/dL) on admission and after 72-96 hours from stroke onset.

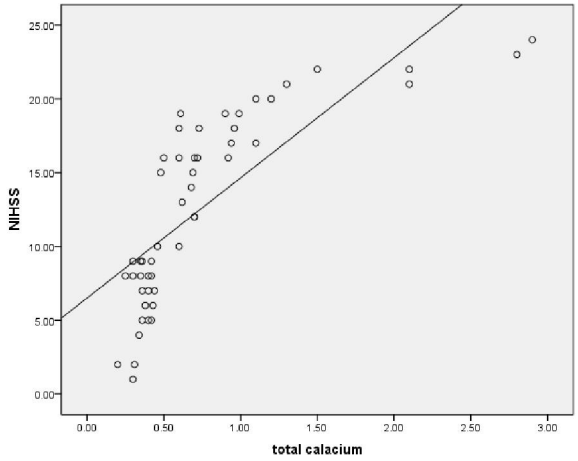

Figure (3): Correlation between total calcium and NHSS

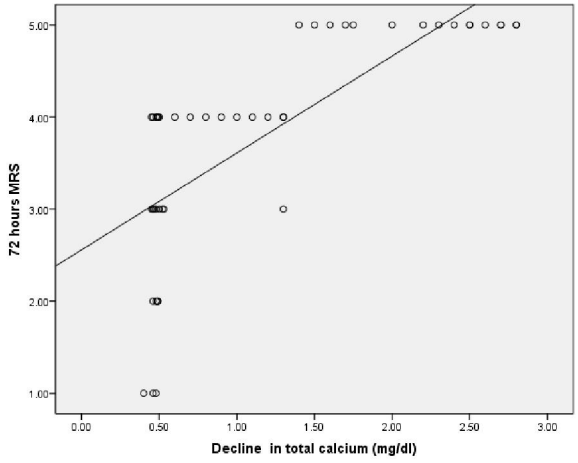

Figure (4): Correlation between 72 hours MRS and decline in total calcium (mg/dl)

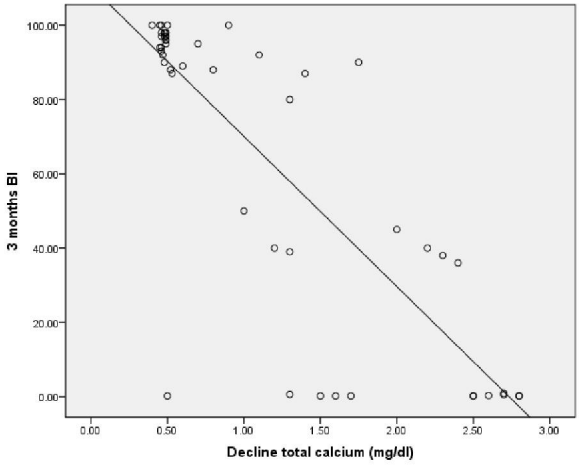

Figure (5): Correlation between 3 months BI and decline in total calcium (mg/dl).

4. Discussion

The present study was concerned with studying the effect of ischemic stroke on serum calcium and the prognostic significance of serum calcium in ischemic stroke. It showed that serum calcium was declined over the first few days after ischemic insult and the more decreased the serum calcium, the more severe the stroke and the bad the outcome.

Many few studies were concerned with studying the same subject. In agreement with the present analysis, a prior study found that early total calcium is of no prognostic value. Bivariate correlation showed that early total calcium that obtained from the patient within 6 hours after the onset of stroke was very weakly correlated to baseline NIHSS, 72-96 hours NIHSS, ΔNIHSS and 72-96 hours BI, while the level of delayed total calcium; that obtained from the patient 72-96 hours after the onset of stroke; was of prognostic significance. It had stronger correlations with the baseline and 72-96 hours NIHSS, ΔNIHSS, 72 hours and 3 months MRS, and 72 hours and 3 months BI(***Ovbiagele et al., 2006;*** **Kasundra *et al.*,2014; Jeffrey Saver, 2016; Liu *et al.*,2016).**

On the other side, another study was in a disagreement with the present results. It found that total calcium obtained from the patient within the first 24 hours of stroke is of prognostic value. After dividing the studied sample into groups according to the level of admission total calcium there is significant difference in the mean admission NIHSS the studied groups ($p<0.05$) with the highest mean NIHSS score was in the group of lowest total calcium level (***Guven et al., 2011).***

Also, **Chung *et al.*, 2015, Daniel *et al.*,2015 and Pandey *et al.*,2015,** found that elevated albumin-corrected serum calcium levels are associated

with a poorer short-term outcome and greater risk of long-term mortality after acute ischemic stroke.

The observed gap between that study and the present one may be due to the difference in the hypothesis of both studies. We supposed that the occurrence of ischemic stroke exerts an effect on the serum calcium. One of the sequels of ischemic insults of the brain is the calcium overload (accumulation of Ca^{2+} inside the neuronal cells). This intracellular shifting of Ca^{2+} may lead to at least temporary depletion of Ca^{2+} in the serum. So for accuracy in studying the effect of ischemic stroke on serum calcium, the studied sample included only patients with admission eucalcemia while patients who had hypo or hypercalcemia were excluded.

In contrast, the other study supposed that the admission serum calcium exert an effect on the severity of ischemic stroke. This hypothesis was base on that the decreased extracellular calcium is an important factor in the positive feedback mechanism that potentiates the inward serum calcium level currents following ischemic injuries. To precisely approve this hypothesis, the study should designed in a cross-sectional manner to compare the severity of ischemic stroke in the patient groups that include admission eucalcemia, hypercalcemia and hypocalcemia.

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