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Research Article

Correlation of serum calcium levels with severity and functional outcome in acute ischemic stroke patients

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ABSTRACT

Background: The objective of the study was to study the role of serum calcium levels in accessing the severity and functional outcome in the patients of acute ischemic stroke.
Methods: The study included a total of 50 patients of acute ischemic stroke in the age group of 20 to 80 years. The patients were divided into four quartiles as per their serum albumin corrected levels measured during 24 ton 48 hours of incidence of ischemic stroke. The stroke severity was accessed by using National Institutes of Health (NIH) stroke scale and the functional outcome at the time of discharge and after three months of follow up by using modified Rankin scale (mRS). The results were analyzed by using appropriate statistical test.
Results: We found that the patients those in higher calcium quartiles (Q3,Q4) had significantly lesser 24-48 hrs stroke severity as compared to those in lower calcium quartiles (Q1,Q2) i.e. in 72.73% in Q3, and 42.86% in Q4 were in mild NIH scale group as compared to 7.69% in Q2 and 0% in Q1. At the time of discharge and at three months follow up functional outcome was significantly better in higher calcium quartile group when compared to lower quartile (>3 mRS score suggestive of poor outcome in 91.66% of Q1, 76.93% in Q2, 27.27% in Q3 and 7.14% in Q4 at the time of discharge and 83.32% in Q1, 76.93 in Q2, 27.27% in Q3 and 7.14% in Q4 at three months of follow up). The correlation analysis showed that this association was statistically significant (p-value <0.01).
Conclusions: we conclude that 24 -48 hours calcium levels have strong correlation with severity and functional outcome in acute ischemic stroke patients and hence it can be taken as a marker of severity and prognostic factor in these patients.

Keywords: Serum calcium, Acute ischemic stroke, Prognostic factor

INTRODUCTION

Calcium (Ca^2+) is the most abundant mineral in the human body. Approx. 500 mmol of calcium is exchanged between bone and the ECF over a period of twenty four hours.

Calcium (Ca^{2+}) plays a pivotal role in the physiology and biochemistry of organisms and the cell. It plays an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. Many enzymes require calcium ions as a cofactor; those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes, as well as proper bone formation.[1]

Cell calcium metabolism during and immediately after a transient period of ischemia influences the cascade of events that leads to subsequent neuronal injury. For instance, ischemia/hypoxia triggers rapid translocation of

Ca^{2}+ from extracellular to intracellular spaces of cerebral tissues.

Ca^{2}+ has also been studied with regard to its relationship with stroke risk factors and stroke incidence. High dietary intake of Ca^{2}+ has been associated with reduced risk of stroke.[2] To our knowledge, very few attempts have been made to investigate the impact of serum Ca^{2}+ level on clinical outcomes after ischemic stroke. The present study has been done with the aim of determining the role of serum calcium in assessing the severity and prognosis of acute ischemic stroke patients.

METHODS

This study has been conducted in the department of Medicine, LLRM Medical College, Meerut, UP. We studied a total of 50 patients of acute ischemic stroke in the age group of 20-80 years. The patients with hemorrhagic stroke or having a disease significantly affecting serum calcium and albumin levels were excluded from the study.

All the participants after thorough clinical assessment were subjected to NCCT brain /MRI brain, serum calcium levels, serum albumin levels, LFT, KFT, ECG and other investigations appropriate for the individual patient. Serum calcium and albumin levels were measured during 24-48 hrs of incidence of ischemic stroke.

The patients were divided into four quartiles according to albumin corrected calcium quartiles, i.e., Q1 with albumin corrected calcium levels ≤ 8.59 mg/dl, Q2 albumin corrected calcium levels between 8.60-8.99 mg/dl, Q3 albumin corrected calcium levels between 9.00-9.39 mg/dl and Q4 albumin corrected calcium levels ≥9.40 mg/dl.

Stroke severity was assessed using the National Institutes Of Health (NIH) Stroke scale3 and functional outcome at discharge and 3 months follow up after stroke using the modified Rankin scale (mRS).[4] Statistical analysis of the observation findings was done using appropriate statistical tests.

RESULTS

Table 1: Distribution of patients in different calcium quartiles (n=50).

Quartiles	Calcium levels (albumin corrected) in mg/dl	No. of patients	%
Q1	≤8.59	12	24
Q2	8.60-8.99	13	26
Q3	9.0-9.39	11	22
Q4	≥9.40	14	28

Table 2: Mean age and Sex distribution in different quartiles.

S. No.	Calcium Quartiles	No. of patients	Male	Female	Mean age (years)
1.	Q1	12	7 (58.3%)	5 (41.7%)	65.25± 9.25
2.	Q2	13	7 (53.8%)	6 (46.2%)	61.07± 10.63
3.	Q3	11	10 (90.9%)	1 (9.10%)	61.18± 9.48
4.	Q4	14	11 (78.57%)	3 (21.43%)	64.92± 13.21

Of the 50 patients included in the study, the distribution in different calcium quartiles is shown in Table 1. Table 2 shows that the mean age and sex of patients in the study do not vary significantly across the calcium quartiles.

Table 3: Patients with hypertension (HTN) and diabetes mellitus (DM) in different quartiles.

S.No.	Calcium Quartiles	No. of patients with HTN	No. of patients with DM
1.	Q1(n=12)	8(66.67%)	2(16.67%)
2.	Q2(n=13)	9(69.23%)	4(30.76%)
3.	Q3(n=11)	8(72.72%)	3(27.27%)
4.	Q4(n=14)	11(78.57%)	4(28.57%)

Table 4: Quartile distribution according to NIHSS Score (for assessing stroke severity).

Scores / Quartiles	NIHSS Score (Stroke Severity)			
	0-4 (Mild)	5-15 (Moderate)	16-20 (Moderately Severe)	21-42 (Severe)
Q1 (n=12)	0[0%]	3[25%]	3[25%]	6 [50%]
Q2 (n=13)	1[7.69%]	8[61.55%]	2[15.38%]	2[15.38%]
Q3 (n=11)	8[72.73%]	2[18.18%]	1[9.09%]	0[0%]
Q4 (n=14)	6[42.86%]	6[42.86%]	0[0%]	2[14.28%]
Total (n=50)	15[30%]	19[38%]	6[12%]	10[20%]

Table 3 shows that the number of patients who were known case of hypertension and diabetes mellitus were comparable in different calcium quartiles. Chi-square tests were done to find out the association between measured calcium quartiles and presence of hypertension and diabetes mellitus as a baseline variables in the study patients and on analysis, no statistically significant association was found (p=0.92 and 0.86 , respectively). It

shows that presence of hypertension and diabetes mellitus had no effect on calcium levels in study patients.

Table 4 shows that the change in values of NIHSS scores is associated with changes in calcium levels in a given quartile. KRUSKAL-WALLIS Test was done for statistical association of stroke severity (NIHSS score) with calcium quartiles and was found to be statistically significant ($p<0.01$).

Table 5 shows that Q1 and Q2 had poor functional outcome than Q3 and Q4 in which the functional outcome was good with normal or high calcium levels in most cases at discharge.

Table 5: Quartile distribution according to mRS Score (for assessing functional outcome) at discharge.

Scores / Quartiles	mRS Score(D): ≤3 Good Outcome/ >3 Poor Outcome					
	1	2	3	4	5	6
Q1(n=12)	0(0%)	1(8.34%)	0(0%)	3(25%)	4(33.33%)	4(33.33%)
Q2 (n=13)	1(7.69%)	1(7.69%)	1(7.69%)	6(46.16%)	3(23.08%)	1(7.69%)
Q3 (n=11)	4(36.37%)	3(27.27%)	1(9.09%)	1(9.09%)	2(18.18%)	0(0%)
Q4 (n=14)	5(35.72%)	7(50%)	1(7.14%)	1(7.14%)	0(0%)	0(0%)
Total (n=50)	10(20%)	12(24%)	3(6%)	11(22%)	9(18%)	5(10%)

Table 6: Quartile distribution according to mRS score after 3 months of stroke.

Scores / Quartiles	mRS Score(After 3 Months): ≤3 Good Outcome/ >3 Poor Outcome					
	1	2	3	4	5	6
Q1 (n=12)	1(8.33%)	0(0%)	1(8.33%)	1(8.33%)	2(16.66%)	7(58.33%)
Q2 (n=13)	1(7.69%)	1(7.69%)	1(7.69%)	3(23.08%)	5(38.46%)	2(15.39%)
Q3 (n=11)	5(45.46%)	2(18.18%)	1(9.09%)	2(18.18%)	1(9.09%)	0(0%)
Q4 (n=14)	10(71.43%)	2(14.29%)	1(7.14%)	1(7.14%)	0(0%)	0(0%)
Total (n=50)	17(34%)	5(10%)	4(8%)	7(14%)	8(16%)	9(18%)

Table 6 also shows that most of the patients in Q1 and Q2 had poor functional outcome than Q3 and Q4 in which the functional outcome was good after 3 months of stroke incidence. Table 5 and 6 show that the change in values of mRS scores at discharge and after 3 months of stroke is associated with changes in calcium levels in a given quartile. The overall mean mRS scores is >3 in first and second quartiles, which suggests poor functional outcome and <3 in third and fourth quartiles which suggests good functional outcome in both, at discharge and after 3 months of stroke incidence.

KRUSKAL-WALLIS TEST was done for statistical association of stroke outcome (mRS score) at discharge and three month follow up, both, with Calcium quartiles and was found to be statistically significant ($p<0.01$).

One way ANOVA test done to find out the association of calcium quartiles with age and Chi-square test for the analysis of calcium quartiles with sex; associations were found to be statistically insignificant (p value=0.74 and 0.16, respectively).

The correlation analysis of 24-48 hr Calcium levels was done which showed definite correlation with stroke severity (NIHSS score) and stroke outcome (mRS Score) ($p<0.01$), but not with other baseline variables in the study patients. Pearson correlation coefficient of calcium levels with NIHSS score was -0.46 which signifies that as calcium levels goes up, severity of stroke went down or vice versa. Similarly, Pearson correlation coefficient of calcium levels with mRS scores was - 0.66 (on discharge) and -0.69 (at 3 months follow up) which again signifies that as calcium levels goes up, the functional outcome got better at discharge and during follow up in the study patients or vice versa.

Univariate analysis of variance with stroke severity (NIHSS score) as dependent variable and calcium levels, age, HTN and DM as covariates was statistically significant only with calcium levels ($p<0.01$).

Univariate analysis of variance with stroke outcome (mRS score at discharge and 3 months) as dependent variable and calcium levels, age, HTN and DM as covariates was also found to be statistically significant only with calcium levels ($p<0.01$).

On bivariate analysis of 24-48 hr calcium quartiles versus stroke severity (NIHSS score), we found it to be statistically significant ($p<0.01$), which means that the stroke severity (NIHSS score) differs significantly with calcium quartiles and it is easy to see that median NIHSS score is higher in the first two quartiles (Q1and Q2) and lower in the last two quartiles (Q3 and Q4).

Also the bivariate analysis of 24-48 hr calcium quartiles versus stroke outcome (mRS score) at discharge and after 3 months of stroke showed to be statistically significant ($p<0.01$) which suggests that mRS score at discharge and after 3 months of stroke differ significantly with calcium quartiles.

Multivariate analysis of variance with age, HTN and DM as covariates and NIHSS score, mRS score (at discharge and 3 month follow up) and serum calcium levels as dependent variables was done and found to be statistically insignificant with all covariates

Finally one way ANOVA was done to test the NULL hypothesis that there is no difference of means of stroke severity (NIHSS score)and outcome (mRS score) across calcium quartiles and it was found that there was a statistically significant difference between means of NIHSS score and mRS score across calcium quartiles(p value <0.1).

DISCUSSION

Calcium (Ca^{2}+) ions play a physiological role in the multiple pathomechanisms of cerebral ischemia.[5,6] Ca^{2}+ has been studied with regard to its relationship with stroke risk factors and stroke incidence. It has been demonstrated that the calcium levels are decreased in cerebral ischemia.[6] It has also been emphasized that gross brain damage, involving edema formation and infarction, is enhanced by tissue acidosis, and that neuronal damage, often showing a pronounced selectivity in localization, appears related to a disturbed Ca^{2}+ homeostasis, and to Ca^{2}+ triggered events such as lipolysis and proteolysis.[7]

It has been found that higher serum calcium levels at admission are associated with smaller cerebral infarct volumes among patients with acute ischemic stroke. The impact of both early and delayed Ca^{2}+ levels on clinical outcomes from acute ischemic stroke has also been studied but no significant outcome differences were noted among early Ca^{2}+levels.[8-10]

In the present study, we took albumin corrected calcium levels of 50 patients of acute ischemic stroke during 24-48 hrs of incidence of the stroke event of both male and female sex, both of comparable ages. We found that Ca^{2}+ levels those in the highest Ca^{2}+ quartile (≥9.40 mg/dl) had significantly lesser stroke severity and better functional outcome than those in lowest Ca^{2}+quartile (≤ 8.50 mg/dl). Also results of correlation analysis showed that 24-48 hr Ca^{2}+ levels has strong correlation with stroke severity and functional outcome at discharge and after 3 months of ischemic stroke.

Clarifying the exact patho-physiological mechanism that may underlie these clinical observations has been challenging, especially because it is unclear whether serum Ca^{2}+ level exerts a primary effect on ischemic stroke or if it reflects a secondary epiphenomenon of ischemic stroke severity. However, our study's findings of prognostic significance for 24-48 hr Ca^{2}+ suggest that the truth may be closer to the latter. Animal studies have shown that Ca^{2}+ movement from serum to brain occurs primarily via the choroid plexuses and when neurons (and/or glia) are exposed to lipid peroxidation, their intracellular structures lose their protection from the extracellular space and a Ca^{2}+ sink is created. As a result more calcium is extracted from the blood into the brain. In order to pull Ca^{2}+ from the serum, the gradient must be sufficient to reduce the content of Ca^{2}+ in the serum. It is thought that total neuronal cell Ca^{2}+ content may increase to 150% of control or more. Furthermore, the finding of more substantial decreases in calcium levels of ischemic stroke patients than of transient ischemic attack and controls may also support this hypothesis. However, whether the amount would be sufficient to change the serum levels to the degree noted in our study is unknown. A comparison of MR images quantifying the extent of brain injury or measurement of Ca^{2}+ concentration in the cerebrospinal fluid versus serum Ca^{2}+ levels would provide insight as to whether greater cerebral damage is associated with lower Ca^{2}+ levels. Calcium channel blockers are extensively evaluated in acute stroke with the hope that stemming excessive cellular calcium influx caused by ischemia might prevent neuronal injury.[11]

Interestingly, the potential role of serum calcium as a clinical prognosticator is not limited to ischemic stroke.[12] Studies of general medical conditions, particularly among the critically ill, have shown that those with hypocalcemia tend to be more severely ill, and have higher mortality rates than those with normocalcemia. We did not have information on medical complications after the strokes in the trial, and so it is conceivable that the 24 to 48 hour Ca^{2}+ levels we observed may have been influenced by the subsequent development of intercurrent illnesses.[13-15]

CONCLUSION

We conclude that the stroke severity and functional outcome differ significantly with calcium quartiles. The severity of stroke is more at low calcium levels than at higher calcium levels and vice versa. Similarly the functional outcome also gets better as the calcium level goes up. This association between calcium levels with stroke severity and functional outcome is independent. These results suggest that serum calcium levels may serve as a marker of severity and also as a prognostic factor following acute ischemic stroke and may be a

potential therapeutic target for improving ischemic stroke outcome.

Limitations of the study

We did not collect data on ionized Ca^2+, which is the physiologically active component of serum Ca^2+ levels. Additionally, we were constrained by lack of stroke subtyping information because small-vessel disease stroke subtype may carry a better prognosis than other subtypes. We also lacked brain-imaging data to investigate the relationship between infarct volume and serum Ca^2+ level.

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