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Original Research Article

A PROSPECTIVE STUDY OF SERUM CALCIUM AS PROGNOSTICATOR OF OUTCOME AND SEVERITY IN ACUTE ISCHEMIC STROKE

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Abstract

Background: Ischaemic stroke is the 2nd leading cause of death worldwide. Ischaemic neuronal death in stroke involves several terminal pathways, including loss of ionic homeostasis. This study was performed to estimate serum calcium levels in patients with acute ischaemic stroke and assess the relationship between calcium levels and the severity of stroke and infarct volume. **Material and Methods:** This prospective study was conducted on 100 patients at the Kanyakumari Government Medical College, Nagercoil, for one year (August 2021 to July 2022). The patients were divided into three groups based on the severity of stroke according to NIHSS admission scores, and their serum albumin-corrected calcium levels measured at admission and 48-72 hours after stroke onset were compared along with cerebral infarct volume (CIV) on neuroimaging. After three months of follow-up, functional outcomes were assessed using the modified Rankin Scale (mRS). **Results:** Delayed calcium (48-72 hours) correlated statistically significantly with stroke severity, functional outcomes, and cerebral infarct volume. Higher serum calcium levels were correlated with better prognosis and lower infarct volumes. Serum Calcium levels measured at admission were not correlated with functional outcomes or cerebral infarct volume. There was no correlation among patients with dietary calcium intake or the use of calcium channel blockers among any of the outcome measures. **Conclusion:** Serum calcium levels may serve as a marker of severity and prognostic factor following acute ischaemic stroke and may be a potential therapeutic target for improving ischaemic stroke outcomes.

INTRODUCTION

The American Stroke Association defines ischaemic stroke as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.[1] It is a rapidly developing focal or global loss of brain function, with symptoms lasting more than 24 hours, leading to neuronal death, with no apparent cause other than that of vascular origin. Stroke is the second leading cause of death worldwide.[2] Approximately 87% of all strokes are ischaemic.[3] ischaemic stroke is characterised by a sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Acute ischaemic stroke is caused by thrombotic or embolic occlusion of the cerebral artery and is more common than haemorrhagic stroke. There is a wide range of severity, from recovery in a few days through persistent disability to death. Globally, approximately 15 million new acute stroke events occur every year. Two-thirds of these individuals live in low-and middle-income countries such as India.[4]

Ischaemic neuronal death in stroke involves several terminal pathways, including loss of ionic homeostasis. Calcium ions play a physiological role in the multiple pathophysiological mechanisms of cerebral ischaemia. Cell calcium metabolism during and immediately after a transient period of ischemia influences the cascade of events that leads to subsequent neuronal injury.[5] Awareness of the participation of Ca2+ in the ischemic cascade has led to the development of several potential neuroprotective agents designed to modify the role of this ion in acute focal brain injury. Ca2+ has also been studied for its relationship with stroke risk factors and stroke incidence.[6]

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To investigate the effect of serum Ca2+ on clinical features of ischaemic stroke, the association of serum Ca2+ levels measured on admission and–48-72 hours after admission, with the severity of symptoms on admission and the short-term prognosis, was evaluated in this study. Elevated serum calcium levels at admission in stroke patients have been associated with less severe clinical deficits and better outcomes. However, the relationship between serum calcium levels and volumetric measurement of cerebral infarct size on neuroimaging has not been conclusively studied.[7]

Aim

This study assessed the relationship between serum calcium levels at admission and CT infarct volume in patients with acute ischaemic stroke.

MATERIALS AND METHODS

This prospective study was conducted on 100 patients at the Kanyakumari Government Medical College, Nagercoil, for one year (August 2021 to July 2022). The study received institutional ethics committee approval before its initiation, and informed consent was obtained from all patients.

Inclusion Criteria

All patients aged > 18 years who were confirmed to have an acute ischaemic stroke by computed tomography/magnetic resonance imaging were included.

Exclusion Criteria

All patients who were previously diagnosed and treated, all patients diagnosed with haemorrhagic stroke or subarachnoid haemorrhage, patients with clinical symptoms of stroke but no signs on CT/MRI, patients with collagen vascular diseases, active tuberculosis, arteritis, patients with h/o head injury within the past three months, patients with any malignant growth, meningitis, brain abscess, or any chronic infection, patients who were < 18 years of age, and patients who died within 72 hours of admission were excluded.

Patients were divided into three groups based on their NIHSS scores on admission: group 1: <5 NIHSS score, Group 2:5-15 NIHSS score, and Group 3: >15 NIHSS score. Pre-specified outcome measures were evaluated with very early calcium levels (obtained on admission) and delayed calcium levels (obtained at 72 to 96 hours after stroke onset), including the following: stroke severity on admission (median GCS Score, NIHSS score), stroke severity at 72 to 96 hours (median GCS score, NIHSS score), neurological improvement (median baseline NIHSS score - NIHSS score at 72 to 96 hours), functional activity at 72 to 96 hours (modified Rankin Scale Score), functional activity at three months (modified Rankin Scale Score), cerebral infarct volume (CIV) measured on the NCCT performed at admission, effect of use of CCB's and calcium intake on calcium levels and functional outcomes.

Statistical Analysis

Appropriate statistical analyses were performed. SPSS software (IBM Analytics) was used to conduct statistical analyses. The tables and graphs were generated using Microsoft Excel.

RESULTS

One hundred patients were included; the mean age was 62.7 years, with the youngest being 25 years and the oldest being 85 years. A maximum of 67 patients were admitted between the age group of > 60. A total of 68 male and 32 female patients, and the male-to-female sex ratio is 2.1 :1. Fifty patients were hypertensive, 34 were diabetic, 57 used tobacco in some form (smoking or chewing), 36 were alcoholic, and 38 were previously diagnosed with dyslipidaemia. [Table 1]

Patients with greater stroke severity, as determined by GCS >15 (Group 3), had lower serum calcium values, with a mean of 5.87 at admission and 9.73 at 72 hours. Furthermore, these patients had a significantly ($p<0.05$, 95% Confidence Interval) larger infarct volume on CT neuroimaging. Thirty patients with greater stroke severity, as determined by NIHSS >15 (Group 3), had lower serum calcium values, with a mean of 16.03 at admission and 5.03 at 72 h. Furthermore, these patients had a significantly ($p<0.05$, 95% Confidence Interval) larger infarct volume on CT neuroimaging.

Patients with greater stroke severity, as determined by an mRANKINS score >15 (Group 3), had lower serum calcium values, with a mean of 4.3 at 72 hours and 4.53 at three months. Systolic BP (151.7) and diastolic BP (91) are significantly higher in Group C >15 score group than groups A and B. There was no significant difference in the severity of RBS, SC, TGL, HDL, or albumin levels between groups A, B, and C. At 72 h, the Sr calcium level was also significantly lower in Group C NIHSS >15 group; the mean Sr calcium was 7.86, compared with Group A and B, 9.18, 8.59; this difference was statistically significant. Infarct volume was significantly higher in group C, i.e., 52.82 when compared with other groups A and B, which are 7.91 and 11.03%, respectively; this difference was statistically significant. [Table 2]

Table 1: Demographic data of the study

		Number of patients
Age	<40	13
	41-60	20
	>60	67
Sex	Male	68
	Female	32

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Risk factors	Hyper tension	50
	Diabetes mellitus	34
	Tobacco cons.	57
	Alcoholic	36
	Dyslipidemia	38
CCB usage	Yes	22
	No	78
Dietary calcium	I	57
	A	43

Table 2: Comparison of various factors with severity between the groups

	Severity (NIHSS)			P value
	Group A (<5)	Group B (5-15)	Group C (>15)	
GCS (admission)	13.9±1.185	11.725±1.811	5.867±2.047	<0.001
GCS (72 hours)	15	14.45±1.26	9.733±4.127	<0.001
NIHSS (72hours)	2.433±1.675	3.375±1.564	16.033±6.97	<0.001
NIHSS (A-72 hours)	0.367±1.771	3.925±2.068	5.033±6.003	<0.001
mRANKIN (72 hours)	1.967±0.765	2.6±1.128	4.3±0.651	<0.001
mRANKIN (3 months)	0.8±0.714	1.35±0.736	4.533±1.697	<0.001
Systolic BP	135.7±16.333	152.0±23.337	151.7±21.985	0.003
Diastolic BP	80.7±12.299	88.8±16.823	91±16.682	0.028
RBS	126.8±49.753	155.5±135.421	175.2±92.111	0.194
BU	33.08±16.478	40.41±18.541	54.47±36.264	0.004
SC	1.253±0.752	1.258±0.568	1.307±0.71	0.941
TC	220.249±33.652	209.808±31.443	193.227±41.293	0.014
TGL	152.16±42.99	133.043±50.998	149.45±60.039	0.014
HDL	37.953±8.646	37.252±8.884	39.313±9.648	0.64
LDL	151.863±30.704	145.948±30.745	124.023±28.785	0.001
Serum albumin	3.8±0.528	4.013±0.738	3.637±0.64	0.059
S. Ca (admission)	9.63±0.491	9.092±0.622	8.763±0.995	<0.001
S. Ca (72 hours)	9.18±0.658	8.59±0.819	7.86±1.103	<0.001
Serum CA (admission	9.79±0.57	9.08±0.753	9.05±0.768	<0.001
Serum CA (72 hours)	9.34±0.512	8.58±0.885	8.15±0.909	<0.001
Infarct volume in mm	7.91±9.537	11.03±20.26	52.82±58.8	<0.001

DISCUSSION

In our study, the mean age of the patients admitted was 62.7 years. The maximum number of patients was in the > 60 age group, the distribution of which is similar to other studies conducted in India. It is assumed that the average age of stroke patients in developing countries is usually 15 years younger than that in developed countries. In India, nearly one-fifth of patients with first-ever stroke admitted to hospitals are estimated to be aged 50 years or less. In this study, only 13 patients were aged < 40 years old. The sex ratio was 2.1:1, with male predominance in this study. This ratio is similar to the epidemiology worldwide and in India, with a higher incidence among males. Age, sex, ethnicity, and genetics are non-modifiable risk factors, and because the population is of homogenous origin, differences in ethnicity and genetics were not considered.

In our study, 50% of the patients had hypertension, which was slightly lower than the global average. In a series of patients affected by ischaemic stroke, hypertension was found in 53-68% of patients. Hypertension is the most important modifiable risk factor for any type of stroke, ischaemic or haemorrhagic, and transient ischaemic attack. It accelerates atherosclerosis progression, which is one of the main predictors of ischaemic stroke. In the Framingham Study, most hypertension-related strokes were due to atherothrombotic brain infarctions. Thus, hypertension is a main risk factor not only for hemorrhagic stroke but also, to a similar extent, a risk factor for Ischemic Stroke.

In our study, 34% of patients had diabetes. DM is also a risk factor for ischaemic stroke. In the Honolulu Heart Program, subjects with known diabetes and asymptomatic hyperglycemic showed an increased risk of ischemic stroke, and these associations were independent of age and other vascular risk factors. Prevalence of DM was 18-32% in atherothrombotic infarction, 20-32% in lacunar infarction and somewhat less in cardioembolic one (8-21%), depending on the series.

In our study, 57% of participants consumed tobacco in some form. A meta-analysis concluded that the relative risk of cerebral infarction associated with cigarette smoking is 1.9. Ex-smokers may reduce their risk of stroke to an RR of 1.2, although this RR remains higher in older people.

In our study, 36% of the patients were alcoholic patients. Moderate alcohol consumption is associated with a lower incidence of ischaemic stroke; however, heavy drinkers are at a higher risk of stroke. It has been suggested that recent alcohol consumption may act as a trigger.

In our study, 38% of the patients had dyslipidaemia. In the study by Simons et al., a high LDL cholesterol level predicted ischaemic stroke, but an HDL cholesterol level did not.[8] This lack of consistency has been suggested to be due to the heterogeneity in the pathogenesis of ischaemic

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stroke. Thus, some stroke subtypes are more closely related to hypercholesterolaemia. This fact is reflected in prospective registries of stroke, where dyslipidaemia is described in up to 46% of atherothrombotic infarctions and up to 38% of lacunar infarctions but in less than 20% of cardioembolic infarctions.

In the present study, albumin-corrected calcium levels of 100 patients with acute ischaemic stroke were measured at admission and–48-72 hours after onset. Patients with greater stroke severity, as determined by GCS >15 (Group 3), had lower serum calcium values, with a mean of 5.87 at admission and 9.73 at 72 hours. Furthermore, these patients had a significantly ($p<0.05$, 95% Confidence Interval) larger infarct volume on CT neuroimaging. The results showed that patients with greater stroke severity, as determined by an mRANKINS score >15 (Group 3), had lower serum calcium values, with a mean of 4.3 at 72 hours and 4.53 at three months.

Systolic BP (151.7) and Diastolic BP (91) are significantly higher in Group C >15 score group than in groups A and B. There was no significant difference in the severity of RBS, SC, TGL, HDL, and albumin levels between groups A, B, and C. By severity, Sr calcium level was significantly lower in Group C NIHSS >15 group; the mean Sr calcium level was 8.76 when compared with Group A, and 9.63, 9.02, at the time of admission. This difference was statistically significant. At 72 h, the Sr calcium level was also significantly lower in Group C NIHSS >15 group; the mean Sr calcium was 7.86, compared with Group A and B, 9.18, 8.59; this difference was statistically significant.

Infarct volume was significantly higher in group C (52.82%) than in groups A and B, which are 7.91 and 11.03%, respectively); this difference was statistically significant. Calcium (Ca^{2+}) ions play a physiological role in the multiple pathologies of cerebral ischemia.[9] Ca^{2+} has been studied with stroke risk factors and incidence. It has been emphasised that gross brain damage, involving oedema formation and infarction, is enhanced by tissue acidosis and that neuronal damage, often showing a pronounced selectivity in localisation, appears to be related to disturbed Ca^{2+} homeostasis and Ca^{2+}-triggered events such as lipolysis and proteolysis. 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.[9]

Clarifying the exact pathophysiological mechanism underlying these clinical observations has been challenging, especially because it is unclear whether serum Ca^{2+} levels primarily affect ischaemic stroke or reflect a secondary epiphenomenon of ischaemic stroke severity. Calcium channel blockers are extensively evaluated in acute stroke with the hope that stemming excessive cellular calcium influx caused by ischemia might prevent 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.

Our study found no differences between patients using calcium channel blockers and other antihypertensive medications. The sample size in this study was too small to draw further conclusions, and a larger study group is required to investigate the role of calcium channel blockers further. There was no difference between the dietary calcium intake and the degree or severity of stroke or functional outcomes. There was also no statistically significant difference between the dietary calcium intake and serum calcium values on admission, probably reflecting physiologically the multiple endocrine feedback loops in play. The potential role of serum calcium as a clinical prognosticator is not limited to ischemic stroke. Studies of general medical conditions, particularly among the critically ill, have shown that those with hypocalcaemia tend to be more severely ill and have higher mortality rates than those with normocalcemia.[9]

CONCLUSION

In conclusion, stroke severity and functional outcome differed significantly with calcium levels at 72 h. Stroke severity is higher at low calcium levels than at higher calcium levels and vice versa. Similarly, functional outcomes improved as the calcium level increased. This association between calcium levels, stroke severity, and functional outcome was independent. These results suggest that serum calcium levels may serve as a severity marker and a prognostic factor following acute ischaemic stroke. They may be a potential therapeutic target for improving ischaemic stroke outcomes.

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