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RESEARCH ARTICLE

PROGNOSTIC SIGNIFICANCE OF SERUM CALCIUM LEVEL IN A SAMPLE OF EGYPTIAN PATIENTS WITH INTRACEREBRAL HEMORRHAGE.

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Key words:-

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Abstract

Introduction: Calcium (Ca), which is an essential factor for human life, could play a role in pathophysiology of spontaneous intracerebral hemorrhage (ICH). This prospective study was conducted to assess serum Ca level in a cohort of Egyptian patients with ICH and searching for a possible association between serum Ca and both of hematoma volume and short-term outcome after ICH.

Patients and Methods: This study was conducted at intensive care units (ICU) of neurology department, Zagazig University Hospitals, Egypt. We included ninety patients with spontaneous ICH. All patients were subjected to thorough history taking, general and neurological examination. National Institute of Health Stroke Scale (NIHSS) was done on admission to assess stroke severity. Initial Computed Tomography (CT) scans were done for all patients within the first 24 hours of admission to calculate the hematoma volume. Serum Ca level was measured on admission for all patients. Short-term outcome was assessed using the modified Rankin scale after one month of ICH onset.

Results: Among the ninety cases of ICH, (14.4%) had low serum Ca on admission. Patients with low serum calcium level had a significantly larger initial hematoma volume and higher scores on NIHSS in comparison to ICH patients with normal Ca level. Serum Ca was inversely correlated with hematoma volume ($p < 0.001$), stroke severity ($P < 0.001$) and stroke outcome according to modified Rankin scale.

Conclusion: low serum Ca level on admission was associated with large initial hematoma volume and unfavorable outcome in patients with spontaneous ICH.

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Introduction:-

Spontaneous intracerebral hemorrhage (ICH) is considered as the most catastrophic stroke, it accounts for approximately 15- 20% of all cerebrovascular strokes¹⁻². Being associated with higher morbidity and mortality, it is considered a major public health problem and needs an effective therapy². Accurate identification of predictors of outcome may help optimal beginning time for immediate intervention and management, which might influence early mortality following ICH. Earlier studies have investigated great associations between clinical, laboratory and

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radiographic factors on one hand and outcomes in patients with ICH on the other hand³⁻⁴. One of these factors is the initial Large hematoma volume which could be considered as an independent predictor of mortality and poor neurologic outcome after acute ICH⁵.

Serum calcium (Ca) is an essential factor for human life, it plays a role in the pathophysiology of cerebral ischemia and influences the molecular pathways of ischaemic neuronal death⁶⁻⁷. Previous researchers⁶⁻⁸ had reported an association between serum Ca level and ischemic strokes as it was observed that a high serum Ca level was associated with a small infarct size and less severe ischemic stroke⁷. In addition, Appel et al.,⁹ observed that ischemic stroke patients with high Ca level had a favorable outcome in comparison to those with low Ca level. Moreover, others demonstrated in a previous study that individuals with high dietary Ca intake had a reduced stroke risk¹⁰.

Data from experimental studies showed an association between Ca levels and changes in bleeding and clotting time¹¹⁻¹², thus it was suggested that Ca could play a role in haemostasis in the setting of acute ICH¹³. Recently, few data were published on the relation between serum Ca level and the initial hematoma volume¹⁴ as well as outcomes after ICH¹³⁻¹⁵. However, the underlying mechanisms are poorly understood¹⁴.

The aim of the current study was to assess serum Ca level in patients with primary ICH and searching for a possible association between baseline Ca level and both of hematoma volume and short-term clinical outcome.

Patients and Methods:-

This study was conducted on 90 patients with primary intracerebral haemorrhage (ICH) who were admitted in Intensive Care Unit (ICU) and stroke Unit of Neurology Department, Zagazig University Hospitals during the period from July 2015 till April 2016. Patients were selected according to the following criteria: patients with ICH who were admitted within 24 hours of symptoms onset. Intracerebral haemorrhage was defined as a new and acute (< 24 hours) neurological deficit with compatible brain imaging showing the presence of intracerebral bleeding¹⁶. Patients with ICH secondary to trauma, tumor, vascular malformation, current use of anticoagulation and those with haemorrhagic transformation Excluded from the study.

All patients were subjected to the following: detailed medical and neurological history taking from either patients or relatives with stressing on stroke risk factors, complete general and neurological examination with assessing stroke severity using National Institute of Health Stroke Scale (NIHSS)¹⁷ which was done on admission. Brain Computed Tomography (CT) scans was done within the first 24 hours of symptom onset to diagnose ICH and to calculate the volume of intracerebral hematoma. Hematoma volume was measured on the initial head CT scan with the use of the ABC/2 equation¹⁸, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the approximate number of slices with hemorrhage multiplied by the slice thickness.

Laboratory investigations including Complete Blood Count, blood glucose level, liver and kidney functions, lipid profile. Assessment of total serum calcium level was done on admission for all patients from venous blood samples. Low calcium level was considered when total serum calcium was less than 8.6 mg/dl according to the reference range of our laboratory. Informed consent from patients or their relatives about the study were obtained. This study was approved by the local ethical committee of Zagazig university hospitals.

Short term outcome was evaluated for the surviving patients after one month from ICH onset using modified Rankin scale¹⁹ which estimates the patient disability with a score ranging from 0 to 6 patients with a score of 0-2 had a favorable outcome. Those with a score of more than 2 considered unfavorable outcome.

Statistical Analysis:-

We used SPSS version 20 software package²⁰ for data analysis. Quantitative variables were expressed as mean \pm SD whereas qualitative variables were expressed as number and percentage. Comparison between groups was done using Chi-square test (χ^2 test) or Fisher exact for categorical variables and Student t-test for continuous variables. Correlations between continuous variables were assessed by Spearman correlation coefficient. P-value < 0.05 was considered significant.

Results:-

A total of ninety patients with a mean age of 68.11 ± 10.79 years were included in this study, Fifty –six were men and thirty-four were women. According to the serum Ca level, we had two main groups: a group of ICH patients with low calcium level < 8.6 mg/dl which included 13 patients (14.4 %). The other group consisted of patients with Ca level ≥ 8.6 mg/dl. Baseline demographic and clinical characteristics according to Ca levels were listed in Table 1. There was no significant difference between those with low and normal calcium level groups as regard sex, age or stroke risk factors. Mean hematoma volume was significantly higher in hypocalcemic than did the normocalcemic group (68.23 ± 7.54 versus 24.07 ± 19.52 respectively). The mean NIHSS scores at admission was higher in those with low Ca level than normocalcemic groups denoting that patients with low serum Ca had a severe stroke and more neurological deficit (27.38 ± 5.0 versus 12.23 ± 7.06 respectively). There was a significant inverse correlation between serum Ca levels in all cases of ICH and the following: hematoma volumes ($r = -0.778$, $P < 0.001$); stroke severity ($r = -0.698$, $p < 0.001$); short-term outcome assessed by modified Rankin scale ($r = -0.707$, $p < 0.001$).

Table 1:- Demographic and clinical Characteristics of the studied patients:

Variables	ICH with Ca < 8.6 (N= 13)	ICH with Ca ≥ 8.6 (N= 77)	P- value
Age	67.85 ± 10.52	68.37 ± 11.06	0.87
Sex (M\ f)	7/6	41/36	0.96
Risk factor:			
HPN, n	8	30	0.12
DM, n	6	26	0.38
Dyslipidemia, n	6	30	0.62
Smoking, n	5	28	0.33
At admission :			
Systolic Bl .p	170.43 ± 20.12	168.79 ± 23.54	0.86
Diastolic Bl. P	95.78 ± 10.51	94.95 ± 11.64	0.79
Laboratory findings:			
TG	130.80 ± 41.28	122.40 ± 36.57	0.49
T. cholesterol	190.66 ± 33.50	194.34 ± 27.40	0.71
HDL	37.64 ± 11.92	39.15 ± 12.57	0.67
LDL	117.48 ± 40.82	123.83 ± 35.63	0.29
INR	1.12 ± 0.8	1.10 ± 0.57	0.93

ICH: intracerebral hemorrhage; **HPN:** hypertension; **DM:** diabetes mellitus; **BL.p:** blood pressure; **TG:** triglycerides; **HDL:** high density lipoproteins; **LDL:** low density lipoproteins; **INR:** international normalized ratio

Table 2:- Relation of serum Ca level with hematoma volume, stroke severity and short-term outcome.

Variables	ICH with Ca < 8.6 (N= 13)	ICH with Ca ≥ 8.6 (N= 77)	P
Hematoma volume:	68.23 ± 7.54	24.07 ± 19.52	0.000*
Baseline NIHSS:	27.38 ± 5.04	12.23 ± 7.06	0.000*
m. Rankin scale (mRS):			
Favorable outcome (< 3):	4 (30.8%)	35 (45.5%)	0.37
Poor outcome (≥ 3):	9 (69.2%)	42 (54.5%)	

ICH: intracerebral hemorrhage, **Ca:** calcium, **NIHSS:** National Institute of Health Stroke Scale

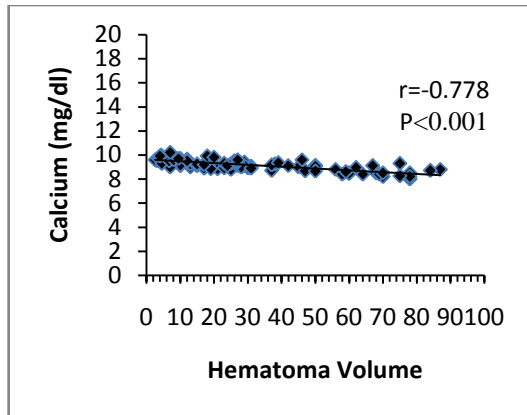


Figure 1:- Correlation between Ca and Hematoma volume.

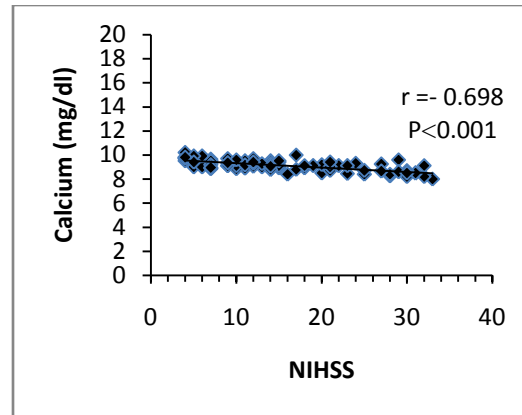


Figure 2:- Correlation between Ca and NIHSS.

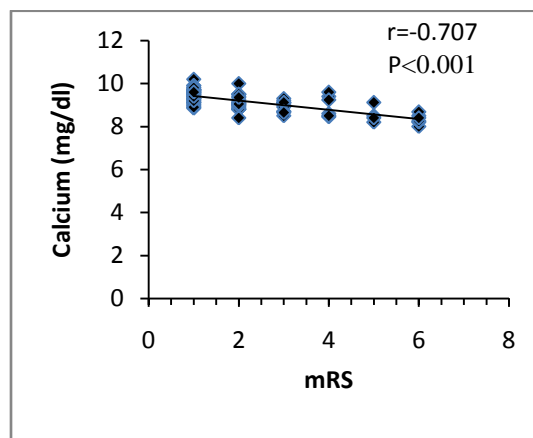


Figure 3:- Correlation between Ca and mRS scale.

Discussion:-

Primary ICH has been reported to be the most devastating form of stroke. It has no proved specific therapy to improve the outcomes according to the results of randomized clinical trials ²¹.

Prognostic laboratory biomarkers have the potential to predict endpoints like complications, mortality, or poor functional outcome in the setting of ICH and therefore may enable preventive and therapeutic interventions ²².

In the current study we investigated the relation between serum Ca level and both of the initial hematoma volume and the short-term outcome in the setting of ICH, as we included (90) patients who were presented with symptoms and CT evidence of ICH and admitted to ICU units of zagazig university hospitals within 24 hours of symptom onset.

This study demonstrated that patients with low Ca level had large initial hematoma volume than did those with normal serum Ca. Furthermore, On studying the correlation between serum Ca in patients with ICH and hematoma volume a significant inverse correlation was observed. Also, the stroke severity was significantly higher in the hypocalcemic than did the normocalcemic group according to the results of admission NIHSS scores. In addition, a negative correlation was observed between serum Ca level and stroke severity scores as assessed by NIHSS.

These findings were matched with the finding of Morroti et al., ¹⁴, who conducted a cohort study of 2123 consecutive patients with ICH, 10.9% of their Patients were hypocalcemic and had a higher baseline hematoma volume than did those with normal serum Ca level. Also they observed a significant inverse correlation between serum Ca and baseline hematoma volume.

Similarly, in (2013) Inoue et al.,¹³ conducted their study on 273 patients with primary ICH and classified their patients into four quartiles according to serum Ca levels. They reported an association between low serum Ca level on admission and initial hematoma volume in patients with acute ICH. Moreover, they demonstrated that the NIHSS scores were higher in patients with the lowest Ca quartile than did patients with the highest Ca quartile group.

Apart from these studies that concerned with ICH, there are similar observations published recently in support of the association between low Ca level and the extent of bleeding. Ho et al.,²³ found that hypocalcemia was associated with increased mortality among patients who were bleeding severely. Another recent study conducted by Ho and Yip²⁴ demonstrated a decreased clot strength in hypocalcemic patients who were either bleeding or at risk of bleeding and they suggested that hypocalcemia could worsen the existing coagulopathy.

Several mechanisms had been postulated to explain the association between low Ca and the extent of intracerebral hematoma. Inuo et al.,¹³ stated that Ca is a cofactor in the coagulation cascade and involved in platelet activation, hence low Ca level is associated with large initial haematoma volume through impaired coagulation.

The second postulated mechanism is that Ca might play a role in vascular reactivity, as stated previously that hypocalcaemia could lead to higher blood pressure. As calcium in its normal levels was reported to induce vascular relaxation of isolated arteries through activation of calcium receptors in the perivascular nerves²⁵. The last proposed mechanism that explains the association between Ca and ICH is that lower serum Ca could reflect a poor liver function as stated by Inuo et al.,¹³ who observed in their study a higher percentage of ICH patients having poor liver function and hence poor coagulation resulting in the large hematoma volume.

The relation between serum Ca and stroke outcomes has been studied previously. It was observed that poor outcome in patients with ischemic stroke was related to lower serum calcium on admission^{6,8,26}. Moreover, previously D'Erasmus and colleagues²⁷ recorded that low serum Ca was associated with in-hospital mortality among ischemic stroke patients. Furthermore, data from large epidemiological studies^{10, 28} had showed that dietary calcium intake was associated with reduced mortality after stroke.

In the current study we assessed the relation between serum Ca and short term outcome after one month of stroke onset using modified Rankin scale, we observed that ICH patients who had a low serum Ca developed a high score on mRankin scale than did those with normal Ca levels. In addition, an adverse correlation was observed between serum Ca and modified Rankin scores that means patients with higher serum Ca at admission had an excellent outcome after ICH.

This result was matching with a study conducted by You et al.,¹⁵ in (2015). They studied a total of 365 patients with primary ICH and assessed the relation between serum Ca on one hand and short and long-term outcomes on the other hand. They demonstrated that elevated admission serum Ca level was positively associated with excellent outcome at both discharge and three months after acute ICH.

In line with the current study, Appel and colleagues⁹ had studied 784 consecutive patients with acute strokes including both ischemic and hemorrhagic types. They demonstrated an association between the baseline serum Ca level and stroke severity and outcome. In addition, they concluded that serum calcium concentrations could be considered as a marker of mortality in acute stroke patients.

The exact mechanisms that lie beneath the association between high serum Ca and favorable outcomes are unclear although several hypotheses were suggested. Foley et al.,⁷ suggested that in the setting of neuronal injury that resulted during cerebral ischemia, a more calcium is shifted to the brain from the blood hence Ca could play a neuroprotective role by enhancing the antiapoptotic pathways. Any subtle increase in Ca in the extracellular space leads to activation of intracellular second messenger and initiation of the antiapoptotic mechanisms²⁹. Previously, it was reported that moderate increase in Ca may promote the cell survival programs and potentiates resistance to hypoxia or ischemia through activated protein kinase B and mitogen activated protein kinase extracellular regulated protein pathways³⁰⁻³¹. Another suggested hypothesis was that Ca had a role in maintaining the blood brain barrier integrity, as reported previously that low calcium levels disturb adhesion and tight junctions³²⁻³³ resulting in cerebral edema which in turn leads to poor outcomes³⁴⁻³⁵.

Conclusion:-

Low Serum Calcium level in the setting of ICH is an indicator of large hematoma volume. There is an relationship between serum Ca level and short-term outcome in patients with ICH, hence serum Ca level could be one of the laboratory biomarkers of prognostic significance in the setting of primary ICH. Thus this study recommends starting modifying calcium levels of patients with ICH arriving in the emergency department as soon as possible to improve the clinical outcome.

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