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Original Article

Association of Serum Homocysteine and Magnesium Levels with Risk and Prognosis in Ischemic Cerebrovascular Accidents.

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Keywords:
Ischemic cardiovascular attack, homocysteine levels, magnesium levels, risk factors for CVA.

ABSTRACT

Background:
Cerebrovascular accident (CVA) is the 2nd leading cause of death worldwide with disability-adjusted life years (DALYs) accounting for about 63.48 million post-ischemic CVA survivals. Among many metabolic risk factors for CVA, high homocysteine and low magnesium values are associated with higher risk and poor outcomes. However, few studies are available that analyzed the changes in these parameters in a longitudinal manner, i.e. 3 months and 6 months after initiation of the treatment **Process**.
Materials and Methods: 50 newly admitted cases of ischemic CVA patients and 50 age and sex-matched healthy control subjects were selected following the sample size calculation formula and pre-fixed inclusion and exclusion criteria in this case control, observational longitudinal study. Serum homocysteine and magnesium levels were measured in all study subjects at the time of admission as well as 3 and 6 months post-treatment periods. The mean/median values of the data were compaired at the pre-treatment level and the post treatment levels for any statistical significance.
Results: Serum homocysteine values were significantly higher at the pre-treatment level in the case group in comparison to the control subjects. The 3 and 6 months post-treatment values were also significantly lower in the case group in comparison to their pre-treatment values. However, no such significant difference were observed in case of serum magnesium values. There was also no correlation between the serum values of homocysteine and magnesium at any level.
Conclusion:
We found significantly higher levels of serum homocysteine values in our patient group at the pre-treatment level (Table 1) and also a significant reduction in their values 3 months and 6 months after implementation of the prescribed treatment regimen. However, no difference among the magnesium values was observed at any stage of the present study. Neither, did we observe any significant correlation between the serum magnesium values and homocysteine levels at any stage.

Introduction

Cerebrovascular accident (CVA) is a major global public health problem and is the leading cause of morbidity and mortality worldwide. Globally cerebrovascular accidents or stroke remain the 2nd leading cause of death with almost 11.6% mortality of all deaths. Among different etiologies, the ischemic type of CVA accounts for almost 62.4% of all strokes worldwide[1]. The ischemic CVA is also of great concern in the context of its fateful consequences of redundant disabilities in the subjects who survive its attack which poses a major loss of manpower and financial burden on society[2]. These disability-adjusted life years (DALYs) account for about 63.48 million post-ischemic CVA survivals[1]. The concern for this non-communicable disorder becomes much more evident by a lifetime risk of stroke and ischemic stroke of 24.9 and 18.3% beyond the age of 25 years[3]. The World Health Organization (WHO) has recommended several preventive measures for reducing this by promoting consciousness for early management of hypertension, prevention of smoking

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and unhealthy diet and improving the mental health and status of well-being with a target to reduce its mortality by one-third by the end of 2030[4].

In India, the cumulative incidence of stroke is found to be within a range of 105 to 152/100,000 persons per year with a crude prevalence of stroke varying from 44.29 to 559/100,000 persons in different parts of the country during the past decade. Importantly, this value is higher than those found in the high-income group countries[5].

Keeping this high incidence rate and an endeavour to control its risk for society, it is important to find out its crucial etiological risk factors at the earliest and to manage them effectively.

Among various modifiable and metabolic risk factors of ischemic stroke, hyperhomocysteinemia, even of a mild degree, has been pointed out as one of the crucial risk elements. Hyperhomocysteinemia promotes the incidence of ischemic stroke by several mechanisms which include suppression of nitric oxide from endothelial tissues and platelets, increased production of hydrogen peroxide, decreased synthesis of glutathione peroxidase and promotion of premature cell death by inducing apoptosis[6-10]. Homocysteine has also been reported to inhibit the DNA methyltransferase enzyme that plays an important role in repair of DNA damage and promoting the cell cycle[11]. Hyperhomocysteinemia is thus a crucial contributing factor in the etiopathogenesis and outcome of ischemic stroke.

Magnesium, an important cofactor for several biochemical reactions, has also been found to be a major confounding factor in the prognosis of ischemic stroke[12]. Studies have revealed that lower levels of serum magnesium are associated with poor outcomes including increased mortality in acute ischemic stroke[13, 14]**.** Furthermore, patients with ischemic stroke with higher magnesium levels were found to have a better prognosis (National Institutes of Health Stroke Scale [NIHSS] $\geq$ 10)[15]. However, some human studies could not show any benefit of intravenous magnesium administration in improvement of acute ischemic stroke[16, 17]. Hence, the available facts at present suggests an incomprehensive and conflicted role of magnesium on the etiophathogenesis and prognosis of acute ischemic stroke. Also few studies were available regarding the association between magnesium and homocysteine in acute ischemic stroke. From these lacunae in the present knowledge, we hypothesized that there are changes in homocysteine and magnesium levels both and there is some relationship between these changes in the acute ischemic stroke patients in our study population and accordingly designed it to test our hypothesis.

MATETERIALS AND METHODS:

The present study was undertaken as an longitudinal, observational case control study involving the Dept of Biochemistry and Dept of Neuromedicine of a tertiary care medical college & hospital in West Bengal, India. The study was undertaken during the period of 18 months from Janurary 2000 to June 2001. Clinically and radiologically confirmed cases of newly admitted ischemic CVA patients were recruited in the study using method of convenience with pre-determined inclusion and exclusion criteria. Healthy persons attending the patients were selected as control subjects after matching for age and sex.

Ethical considerations: The whole study was conducted following the Helsinki Declaration and ICMR guidelines for human studies. Institutional Ethics Committee permission was obtained before the start of the study as per protocol.

The inclusion criteria were i) diagnosed cases of Ischaemic cerebrovascular accident confirmed by clinical and radiological means (CT/MRI) ii) age between 30 -80 years, and iii) 3) both male and female patients without any bias.

The exclusion criteria were: i) CVA due to any infectious cause (meningitis, brain abscess), vasculitis or coagulopathy. ii) History of any autoimmune disorder, any vasculitis or any coagulopathy. iii) iatrogenic CVA. iv) use of any medications within last 30 days that could affect total homocysteine level (Methotrexate, Tamoxifen, Levodopa, Niacin or Phenytoin) or bile acid sequestrants that can decrease Vitamin B12, folate levels. v) TIA, recurrent CVA, intracerebral haemorrhage or tumour, subarachnoid haemorrhage, head injury within past 3 month. vi) Admission to hospital after 72 hours of the onset of CVA. vii) Patient on steroids or immunomodulatory drug, viii) Patient is suffering from any infection. ix) Patients with a history of heart disease: any valvular heart disease, infective endocarditis, and myocardial infarction. x) Pregnant and lactating mother. xi) Patient who have developed infection within 72hrs of onset of CVA.

Sample size calculation: The estimated number of samples were calculated by the formula mentioned below.

$n = Z\alpha^2 pq/ (L^2)$ Where, n= required sam ple size, $Z\alpha = 1.96$ at 95% confidence interval (CI) p= 0.154 (as per Indian council for Medical Research, 2006), q= 1-p L= absolute precision (10%).

Following this, 50 cases of ischemic cerebrovascular accident were selected depending on total patients attended in the desired period 50 age and sex matched controls were included in the study. The severity of ischemic cerebrovascular accident in the case group was assessed using NIH Stroke Scale.

Laboratory methodology:

5 ml of blood was collected aseptically from all study subjects in clotted vials and serum was collected. Homocysteine and magnesium were measured from the clotted blood.

Measurement of serum homocysteine: Serum homocysteine was measured by a competitive immunoassay using direct, chemiluminescent technology using ADVIA Centaur automated chemiluminescent analyzer.

Measurement of serum magnesium: Serum magnesium was measured using the KONELAB PRIME 60i Auto analyser. Magnesium assay is a photometric method where magnesium forms a soluble red coloured complex when reacts with Xylidyl-blue in alkaline solution with a maximum absorbance 510 and 520nm. The intensity of the colour formed is proportional to the magnesium concentration in the sample.

Data collection and analysis: All the parameters were assessed in the untreated ischemic cerebrovascular accident cases at admission and 3 and 6 months post-initiation of treatment. All tests were also performed for recruited controls. Data were collected and analyzed for their distribution pattern, i.e., for normal or non-parametric distribution. Statistical analyses were designed accordingly. All data were analyzed using the SPSS software version 24.0 for Windows.

RESULTS:

Following the inclusion and exclusion criteria, 50 cases and 50 control subjects were selected during the study period.

Comparison between serum Homocysteine levels in Cases of Ischaemic cerebrovascular accident with age and sex matched Controls: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were not normally distributed. So, Mann-Whitney U test was applied to compare the serum Homocysteine levels in cases of ischemic cerebrovascular accident with that of the age and sex matched controls and found to be significantly higher in pre-treatment cases than controls.

Table 1: Serum level of Homocysteine (µmol/L) in Pre-treatment Cases and Controls:

		No.	Mean	SD	Minimum	Maximum
Homocysteine (µmol/L) Pre-treatment	Case	50	16.85	11.39	4.200	54.00
	Control	50	10.57	4.537	4.300	27.00

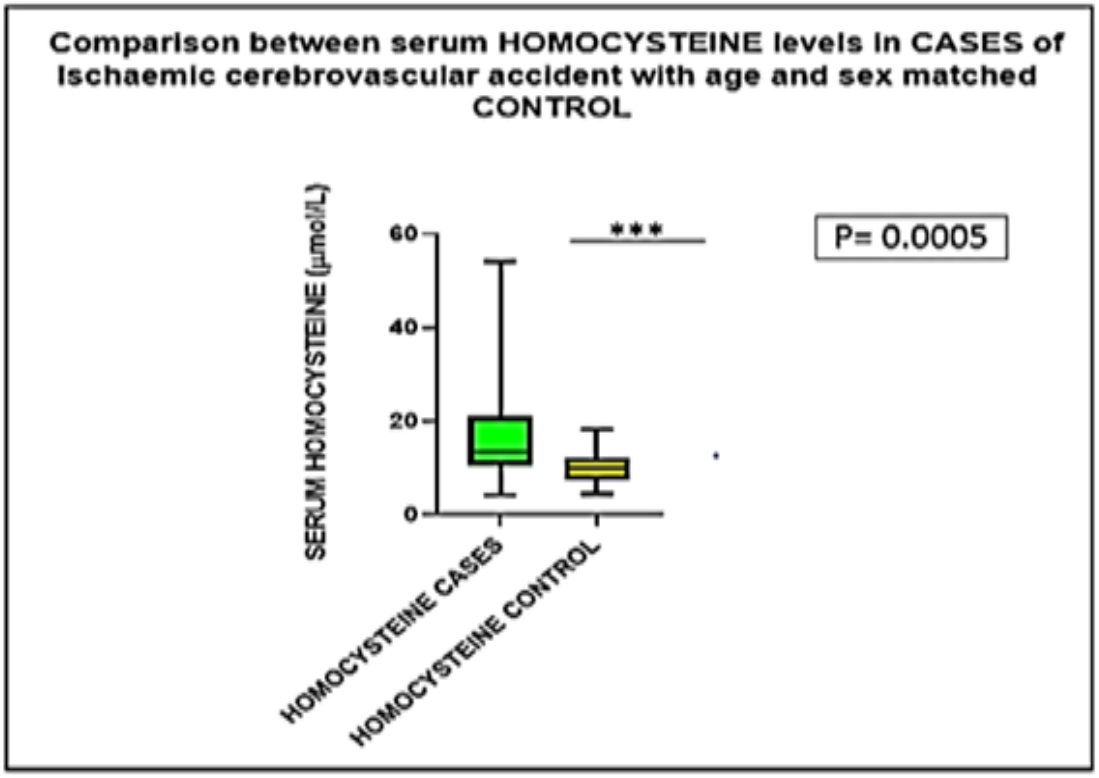

Figure 1 : Box and Whisker plot showing the comparison between serum Homocysteine levels in Cases of Ischaemic cerebrovascular accident (Mean ± SD = 16.85 ± 11.39) with age and sex matched Control (Mean ± SD = 10.57 ± 4.537). Mann-Whitney U test was applied & showed significantly higher level of serum Homocysteine in pre-treatment cases as compared to Controls.

Comparison between serum Magnesium levels in Cases of Ischaemic cerebrovascular accident with age and sex matched Controls: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were normally distributed. So, Unpaired t test was applied for comparing the serum Magnesium levels in cases of ischemic cerebrovascular accident as opposed to that of the age and sex matched controls and found to be not significantly higher in pre-treatment cases than controls.

Table 2: Serum level of Magnesium (mg/dl) in Pre-treatment Cases and Controls were statistically obtained:

		No.	Mean	SD	Minimum	Maximum
Magnesium (mg/dl) Pre-treatment	Case	50	1.965	0.4493	1.170	3.100
	Control	50	1.834	0.2987	1.400	2.500

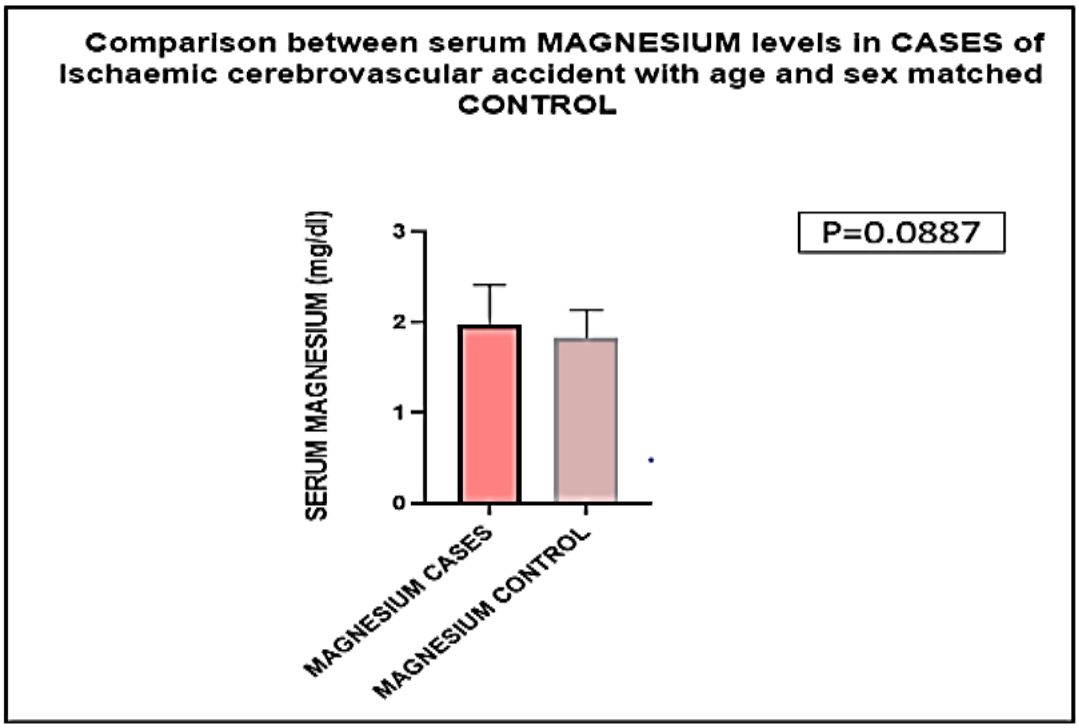

Figure 2 : Bar diagram showing the comparison between serum Magnesium levels in Cases of Ischaemic cerebrovascular accident (Mean ± SD = 1.965 ± 0.4493) with age and sex matched Controls (Mean ± SD = 1.834 ± 0.2987). Unpaired t test was applied & showed not significantly higher level of serum Magnesium in pre-treatment cases as compared to Controls.

Comparison between serum Homocysteine (µmol/L) levels in Pre-treatment and 3 months Post-treatment cases of Ischaemic cerebrovascular accident: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. 29 cases were found to be expired in 3 months follow up. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were not normally distributed. So, Wilcoxon Signed Rank test was applied for comparing the serum Homocysteine levels in Pre-treatment cases and 3 months Posttreatment cases of ischemic cerebrovascular accident.

Table 3: Comparison of serum level of Homocysteine (µmol/L) in Pretreatment and 3 months Post-treatment Case

	Cases	No.	Mean	SD	Minimum	Maximum
Homocysteine (µmol/L)	Pre-treatment	50	16.85	11.39	4.200	54.00
	3months Post-treatment	21	10.50	4.702	4.000	22.80

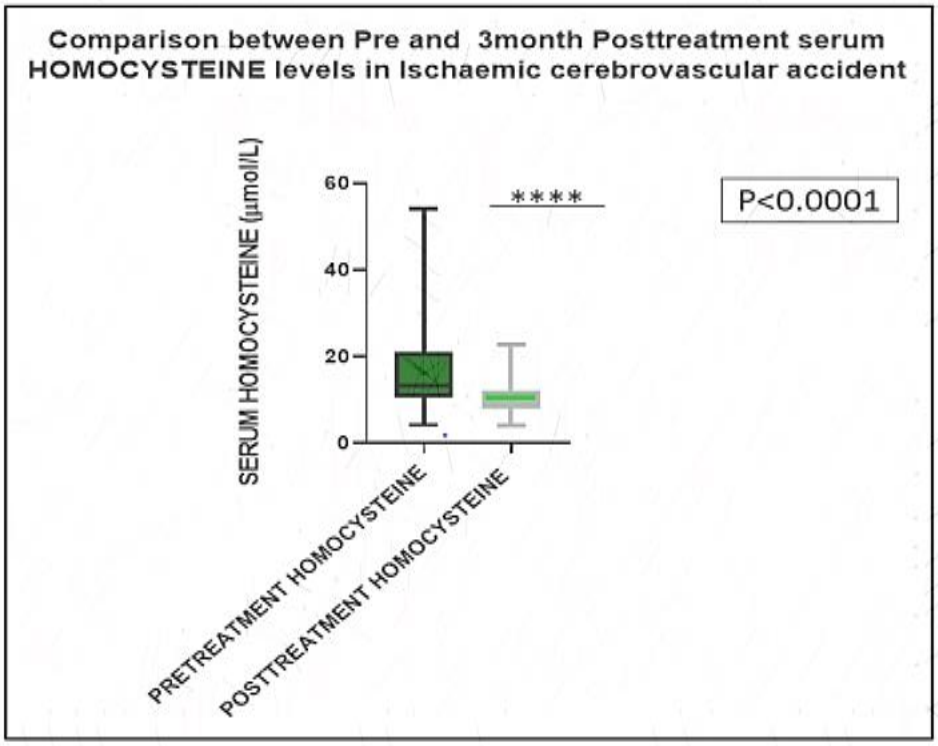

Figure 3 : Box and Whisker plot showing the comparison between Pre-treatment serum Homocysteine levels (Mean ± SD = 16.85 ± 11.39) and 3months Post-treatment serum Homocysteine levels (Mean ± SD = 10.50 ± 4.702) in Cases of Ischaemic cerebrovascular accident. Wilcoxon Signed Rank test applied & showed significant lower level of serum Homocysteine in 3months Post-treatment cases as compared to Pre-treatment cases.

Comparison between serum Magnesium (mg/dl) levels in Pre-treatment and 3 months Post-treatment cases of Ischaemic cerebrovascular accident: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. 29 cases were found to be expired in 3 months follow up. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were normally distributed. So, Paired t test was applied for comparing the serum Magnesium levels in Pre-treatment cases and 3 months Post-treatment cases of ischemic cerebrovascular accident.

Table 4: Comparison of serum level of Magnesium (mg/dl) in Pretreatment and 3 months Post-treatment Cases:

	Cases	No.	Mean	SD	Minimum	Maximum
Magnesium (mg/dl)	Pre-treatment	50	1.965	0.4493	1.170	3.100
	3months Post-treatment	21	1.918	0.2698	1.500	2.500

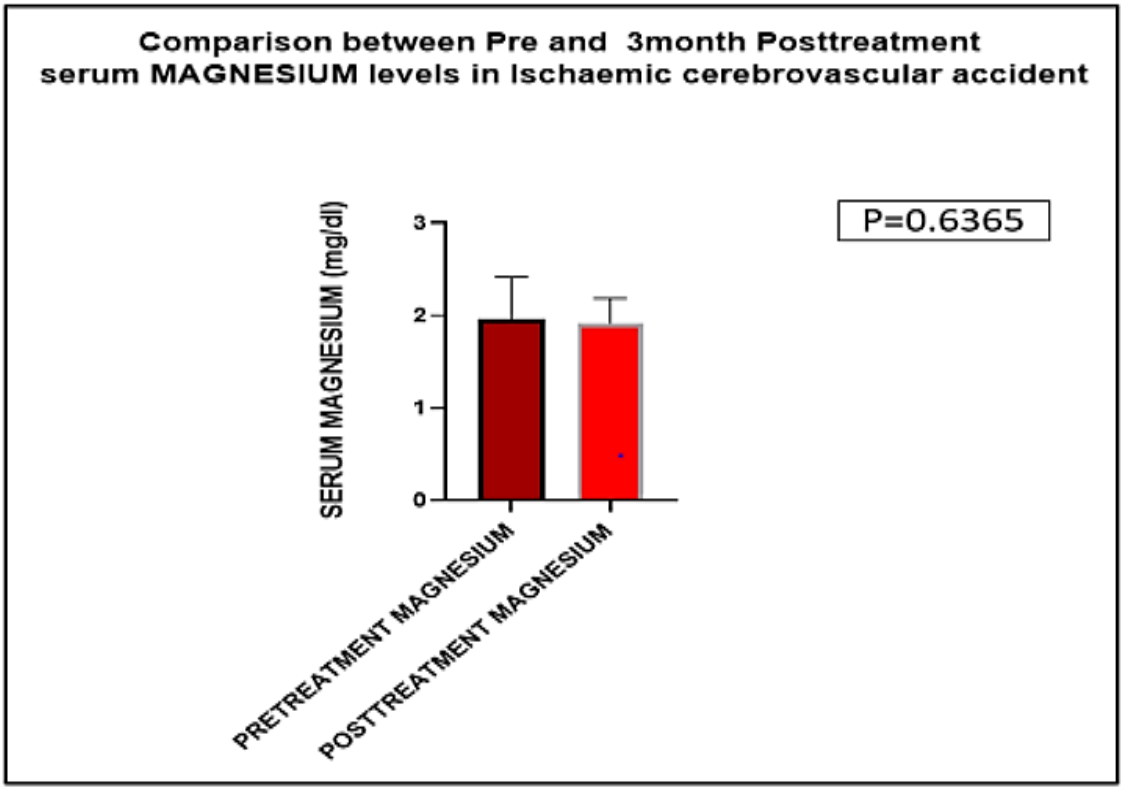

Figure 4 : Bar diagram showing the comparison between Pre-treatment serum Magnesium levels (Mean ± SD = 1.965 ± 0.4493) and 3months Post-treatment serum Magnesium levels (Mean ± SD = 1.918 ± 0.2698) in Cases of Ischaemic cerebrovascular accident. Paired t test applied & showed not significant lower level of serum Magnesium in 3months Post-treatment cases as compared to Pre-treatment cases.

Comparison between serum Homocysteine (µmol/L) levels in Pre-treatment and 6 months Post-treatment cases of Ischaemic cerebrovascular accident: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. 29 cases were found to be expired in 6 months follow up. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were not normally distributed. So, Wilcoxon Signed Rank test was applied for comparing the serum Homocysteine levels in Pre-treatment cases and 6 months Posttreatment cases of ischemic cerebrovascular accident.

Table 5: Comparison of serum level of Homocysteine (µmol/L) in Pretreatment and 6 months Post-treatment Cases:

	Cases	No.	Mean	SD	Minimum	Maximum
Homocysteine (µmol/L)	Pre-treatment	50	16.85	11.39	4.200	54.00
	6months Post-treatment	21	9.339	2.548	5.000	14.90

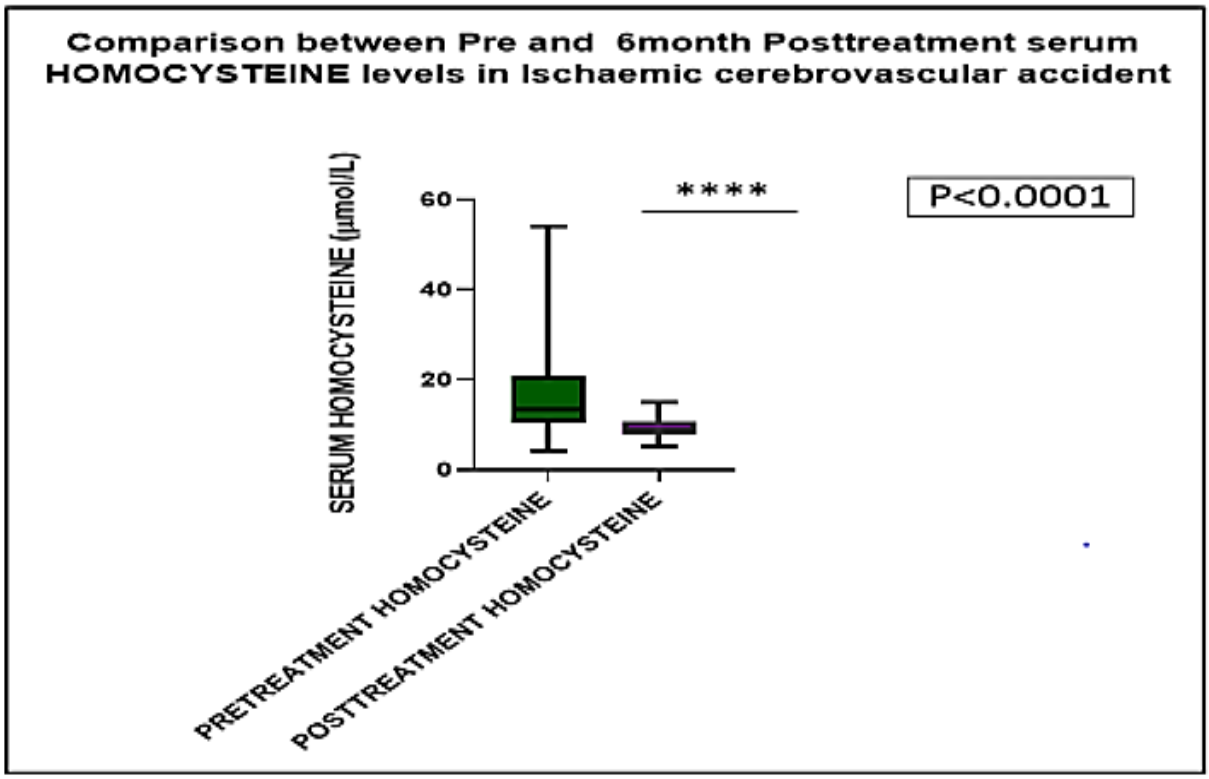

Figure 5. : Box and Whisker plot showing the comparison between Pre-treatment serum Homocysteine levels (Mean ± SD = 16.85 ± 11.39) and 6months Post-treatment serum Homocysteine levels (Mean ± SD = 9.339 ± 2.548) in Cases of Ischaemic cerebrovascular accident. Wilcoxon Signed Rank test applied & showed significant lower level of serum Homocysteine in 6months Post-treatment cases as compared to Pre-treatment cases.

Comparison between serum Magnesium (mg/dl) levels in Pre-treatment and 6 months Post-treatment cases of Ischaemic cerebrovascular accident: 50 cases of clinically and radiologically (CT/MRI) diagnosed ischemic cerebrovascular accident were taken. 29 cases were found to be expired in 6 months follow up. Normality of the sample size was tested with the D'Agostino & Pearson omnibus normality test. It was observed that the data were normally distributed. So, Paired t test was applied for comparing the serum Magnesium levels in Pre-treatment cases and 6 months Post-treatment cases of ischemic cerebrovascular accident.

Table 6: Comparison of serum level of Magnesium (mg/dl) in Pretreatment and 6 months Post-treatment Case

	Cases	No.	Mean	SD	Minimum	Maximum
Magnesium (mg/dl)	Pre-treatment	50	1.965	0.4493	1.170	3.100
	6months Post-treatment	21	1.869	0.1230	1.600	2.100

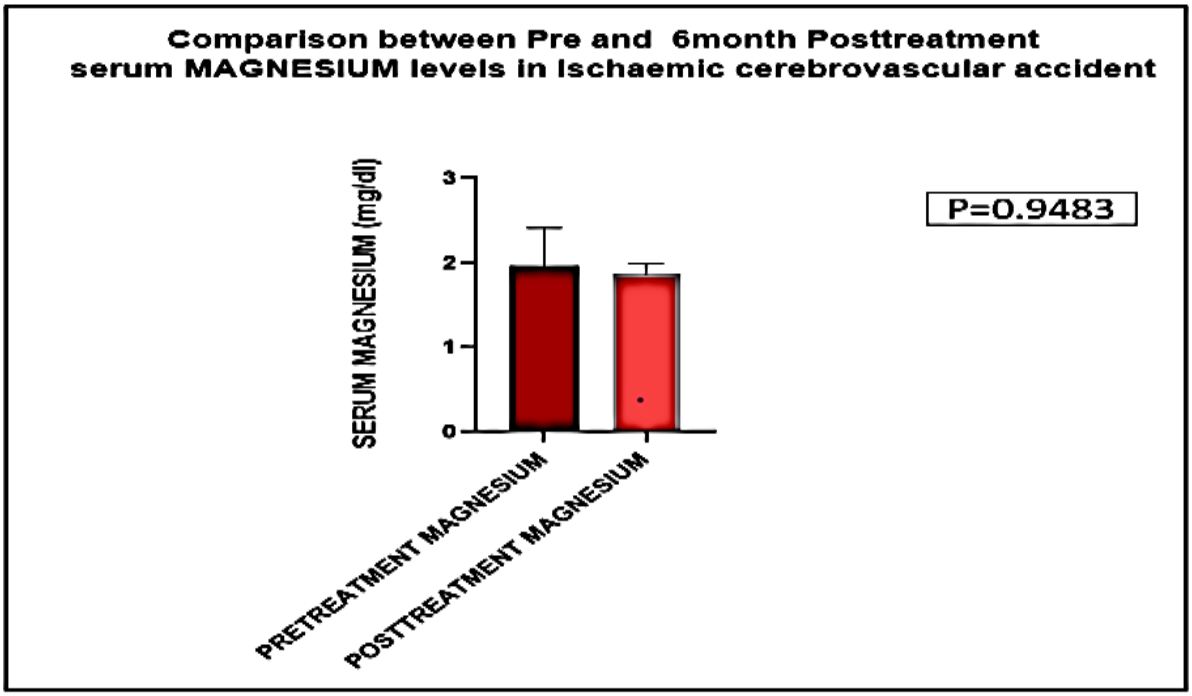

Figure 6 : Bar diagram showing the comparison between Pre-treatment serum Magnesium levels (Mean ± SD = 1.965 ± 0.4493) and 6months Post-treatment serum Magnesium levels (Mean ± SD = 1.869 ± 0.1230) in Cases of Ischaemic cerebrovascular accident. Paired t test applied & showed not significant lower level of serum Magnesium in 6months Post-treatment cases as compared to Pre-treatment cases.

DISCUSSION:

Ischemic cerebrovascular accident is the most common type of cerebrovascular accident which accounts for about 80%–85% of cerebrovascular accident cases.

Tan et al studied young adult Asians with ischemic cerebrovascular accident and found a strong relationship between increased serum Homocysteine level and ischemic cerebrovascular accident[18]. Biswas et al conducted a study in 120 Indian patients with acute ischemic cerebrovascular accident and showed that there was a significant relationship between serum Homocysteine level and ischemic cerebrovascular accident[19]. In our study Mann-Whitney U test was applied and showed a significantly higher level of serum Homocysteine levels in pre-treatment Cases (Mean ± SD = 16.85 ± 11.39) as compared to age and sex matched Controls (Mean ± SD = 10.57 ± 4.537, Table 1 and Figure 1). 29 cases were found to be expired in 3 months follow up. Comparison between Pre-treatment serum Homocysteine levels (Mean ± SD = 16.85 ± 11.39) and 3 months post-treatment serum homocysteine levels (Mean ± SD = 10.50 ± 4.702) Wilcoxon Signed Rank 100 test showed significantly lower levels of serum Homocysteine in 3months Posttreatment cases than Pre-treatment cases (Table 3 and Figure 3). Pre-treatment serum Homocysteine levels (Mean ± SD = 16.85 ± 11.39) and 6 months post-treatment serum Homocysteine levels (Mean ± SD = 9.339 ± 2.548) Wilcoxon Signed Rank test showed significantly lower level of serum Homocysteine in 6 months post-treatment cases as compared to pre-treatment cases.

Bonthapally et al showed that serum Homocysteine levels correlated well with the severity of ischemic cerebrovascular accident as assessed by NIHSS[20]. Xu Qing Wu et al also found that acute phase elevation of serum homocysteine levels correlated with severity and prognosis using NIH Stroke Scale and Modified Rankin Scale in patients with atherothrombotic cerebrovascular accident[19]. But our study's Spearman Rank Order Correlation test showed no significant correlation of pre-treatment serum Homocysteine levels with NIH Stroke Scale [p value 0.0815, r = 0.2488]. In a study, Mizrahi et al reported that elevated serum Homocysteine levels do not serve as a predicting factor for functional outcome at discharge and rehabilitation gains after 6 months in ischemic cerebrovascular accident [21]. The present study showed no significant correlation of 3 months Post-treatment serum Homocysteine levels with Modified Rankin Scale [Spearman Rank Order Correlation test: p value = 0.3376, r = 0.2202].

Serum Magnesium possibly decreases neuronal damage in cerebral ischemia by various mechanisms such as inhibition of ischemia-induced glutamate release, NMDA receptor antagonism, blocking calcium entry into the cells and buffering of excessive calcium, preventing depletion of ATP, and also by increasing cerebral blood flow[22]. Low serum Mg^{2+} level at the time of cerebrovascular accident may accelerate penumbral compromise and result in more severe cerebrovascular accident presentations or early neurologic deterioration if not replaced with magnesium therapy[23].

A study by Kaur et al (2012) found that the serum magnesium levels were significantly lower in cerebrovascular accident patients and the serum magnesium levels were not significantly higher in a hemorrhagic cerebrovascular accident when compared with ischaemic cerebrovascular accident [24]. Siegler et al (2013) assumed that higher serum magnesium levels may contribute to improved outcomes following an ischaemic cerebrovascular accident, possibly related to vessel recanalization [25]. Cojocaru et al found lower serum magnesium levels in patients of ischemic cerebrovascular accident as compared to controls and also a lower level in patients with higher degree of neurological disability[26]. In this study unpaired t-test was applied between serum Magnesium levels in Cases (Mean ± SD = 1.965 ± 0.4493) with age and sex-matched Controls (Mean ± SD = 1.834 ± 0.2987) which showed no significantly higher level of serum Magnesium in pre-treatment cases as compared to Controls. Also, the Paired t-test comparison between Pre-treatment serum magnesium levels (Mean ± SD = 1.965 ± 0.4493) and 3 months post-treatment serum Magnesium levels (Mean ± SD = 1.918 ± 0.2698) in Cases showed no significantly lower level of serum Magnesium in 3 months Post-treatment cases where 29 cases were found to be expired in 3 months follow up. Comparison between Pre-treatment serum Magnesium levels (Mean ± SD = 1.965 ± 0.4493) and 6 months Post-treatment serum Magnesium levels (Mean ± SD = 1.869 ± 0.1230) in Cases showed no significant lower level of serum Magnesium in 6 months Post-treatment cases as compared to Pre-treatment cases. Siegler et al found a relationship between magnesium levels at baseline and magnesium replacement with NIHSS over time [108]. In the present study pretreatment serum Magnesium levels according to NIHS scale of performance status in cases showed no significant correlation of pre-treatment serum Magnesium levels with NIHS scale [Pearson Rank Order Correlation test p value 0.1535, r = 0.2049]. Ovbiagele et al did not find any relation between pre-treatment serum magnesium levels and severity of cerebrovascular accident [27]. Saberi et al found a reciprocal correlation between serum magnesium levels and neurological disability [28]. In our study, serum magnesium levels according to Modified Rankin Scale of performance status in cases showed no significant correlation of 3 months Post-treatment serum Magnesium levels with Modified Rankin Scale [Pearson Rank Order Correlation test: p value = 0.7163, r = -0.08434]. and also in 6 months Post-treatment serum Magnesium levels according to Modified Rankin Scale of performance status in cases showed no significant correlation [Pearson Rank Order Correlation test: p value = 0.8442, r = 0.04566].

CONCLUSION:

In conclusion, keeping in track with previous results we found significantly higher levels of serum homocysteine values in our patient group at the pre-treatment level (Table 1) and also a significant reduction in their values 3 months and 6 months after implementation of the prescribed treatment regimen. However, no difference among the magnesium values was observed at any stage of the present study. Neither, did we observe any significant correlation between the serum magnesium values and homocysteine levels at any stage. To the best of our knowledge, very few studies were carried out to delineate the relationship between these two serum biomarkers i.e. homocysteine and Magnesium with 3 & 6 months follow-up of ischemic cerebrovascular accident. To prove the independent association between biomarker level and poor outcome, we strictly selected the inclusion and exclusion criteria to obtain homogenous data and to avoid potential confounding factors.

From all observations and their analysis, we may conclude that serum homocysteine is not only a valid tool for assessing the risk of ischemic CVA, but can also be used to assess the prognosis of the illness 3 months and 6 months after starting its treatment. However, serum magnesium did not show any such risk assessment or prognostic value for the ischemic CVA in our present study.

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