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Effect of Serum Magnesium Level on Short Term Outcome of Different Types of Acute Stroke in a Tertiary Level Hospital in Bangladesh

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Abstract: ***Background: Magnesium (Mg2+) has shown to have important effect in vascular system, and thought to be a risk factor for ischemic stroke and linked the outcome of intracerebral hemorrhage. However, very limited evidence was sought particularly in our country perspective. Methods: This hospital based cross-sectional study was conducted at the Department of Medicine in Dhaka Medical College Hospital, for a period of 6 months from October 2018 to March 2019. Patients with acute stroke were included into the study after confirmation of the diagnosis and matching other selection criteria. Written informed consents were taken from the all study subjects and ethical issues were ensured. Data were collected by interview using a semi-structured questionnaire. Short term outcome assessment was done by Modified Rankin Scale (MRS). Results: Among 100 patients, 58% were males and 42% were females. Mean age was 60.46 (±10.14 SD) years and prevalent (48%) age group 61-70 years. Of all, 42% were diagnosed as ischemic stroke, 40%-intracerebral haemorrhage and 18% were subarachnoid hemorrhage. Hypomagnesemia was present in 59.5% of ischemic stroke patients whereas it was present in 12.5%& 11.1% cases in hemorrhagic stroke and SAH patients, respectively. Serum magnesium level was significantly lower in ischemic stroke patients in comparison to patients with hemorrhagic stroke and SAH (p<0.001). This hypomagnesemia is related to poor short term outcome in ischemic stroke patients (p<0.05), but not significantly in patients with hemorrhagic stroke and SAH. Conclusion: Hypomagnesemia is more prevalent in ischemic stroke patients than other type of stroke and this lower level of hypomagnesemia also has impact on short-term outcome in ischemic stroke patients.***

Keywords: Stroke, Serum Magnesium, Short Term Outcome

1.Introduction

World Health Organization (WHO) defined stroke as rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin. This definition includes most cases of cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage. [1] Stroke is one of the leading causes of death throughout the world and the predominant vascular disease in many parts of Asia. [2]According to the World Health Organization (WHO), 15 million people suffer stroke worldwide each year. Of these, 5 million die, and another 5 million are left permanently disabled. [3]It is estimated that by 2030, 80% of strokes will occur in people living in low and middle income countries, and stroke will account for 7.9% of all mortality in low income countries. The worldwide incidence of stroke has been quoted as 2/1000 population per annum; about 4/1000 in people aged 45-84 years. [4, 5]In India the incidence rate is 119-145/100, 000 per year. [6]In Bangladesh, stroke has been ranked as the third leading cause of death after coronary heart disease and infectious diseases such as influenza and pneumonia. The mortality rate of stroke increased from 6·00% (in 2006) to 8·57%, (in 2011) with an age-adjusted mortality rate of 108·31 per 100 000 people (in 2011). The World Health Organization (WHO) ranks mortality due to stroke in Bangladesh as number 84 in the world.[7]

Magnesium is a biologically essential cation, which has recently received considerable attention in clinical medicine, especially with regard to the role of its depletion in cardiovascular physiology. [8]This element has important effects within the vascular system. Magnesium deficiency was shown to trigger vasoconstriction and enhance vascular endothelial injury, thus promoting the development and progression of atherosclerosis. [9]It has been suggested that magnesium intake or serum magnesium levels are inversely associated with cardiovascular risk factors such as hypertension, type 2 diabetes mellitus and insulin resistance as well as incidence of cardiovascular diseases. [10, 11]

There are numerous possible modes of action for magnesium in protecting neurons and glia from ischemic damage. [12]It is involved in multiple physiological processes that may be relevant to cerebral ischemia, including antagonism of glutamate release, N-methyl-d-aspartate (NMDA) receptor blockade, calcium channel antagonism, and maintenance of cerebral blood flow. [13–16]Moreover, it has been shown to suppress anoxic depolization and cortical spreading depression – both potential targets for neuroprotective treatment. [13, 14, 17, 18]

Magnesium has also shown to play crucial roles in hemostasis by accelerating activation of factor X via factor VII–tissue factor[19], causing conformational changes in coagulation factor IX[20]that augment its biological activities, [21]potentiating platelet aggregation and decreasing levels of the intrinsic anti thrombotics protein S and C. [22]These properties of magnesium may be important in hemorrhagic strokes. Actually it has been shown that in patients admitted with intracerebral hemorrhage, lower admission magnesium levels were associated with larger initial hematoma volumes and worse functional outcomes at 3 months. [23, 24]

The neuroprotective role of magnesium was also found to be important in case of subarachnoid hemorrhage. Poor outcome in subarachnoid hemorrhage is partially attributed to delayed cerebral ischemia (DCI) [25, 26] which occurs most frequently between 4 and 10 days after the hemorrhage[27, 28]. Hypomagnesemia occurs in 50% of patients with SAH and is related to the occurrence of DCI and poor outcome after 3 months[29]. Actually it has been found that intravenous magnesium can reduce cerebral ischemic events after aneurysmal subarachnoid hemorrhage by attenuating vasospasm and increasing the ischemic tolerance during critical hypoperfusion[30] and its effect is comparable with that of Nimodipine. [31]

The aim of this study was to find out serum magnesium level in patients presented with different types of stroke and also to note its association with the short term outcome.

2.Literature Survey

There are a number of studies done all over the world to find out the relationship of serum magnesium level and incidence and outcome of stroke. In a study by Siegler JE et al. in 2013 of total 313 ischemic stroke patient included, 181 (57.8%) were found to have low serum magnesium levels at admission. [32]

Alia Saberi studied in the title of the relationship between magnesium level and first 72 hours Rankin score and Rankin score in 1 week after an ischemic stroke where 67 ischemic stroke patients were included who presented when less than 6 hours had passed from their attacks. Serum magnesium level was measured and correlated with patient's disability in the first 72 hours and 1 week after the stroke. Result showed that there is no correlation with the mean of changes of disability score in this period of time. [33]

Eric M studied 290 patients who presenting with spontaneous intracerebral hemorrhage (ICH). Serum magnesium level was measured at the time of admission. Result found that lower magnesium level was associated with worse functional outcomes at 3 months after adjustment for age, admission Glasgow Coma Scale score, initial hematoma volume, time from symptom onset to initial CT, and hematoma growth. [23]

Nitin Goyal reviewed data on 299 patients with spontaneous intracerebral hemorrhage (ICH) with available Mg levels at baseline, over a 5-year period. Increasing admission Mg levels strongly correlated with lower admission National Institutes of Health Stroke Scale (NIHSS) score, lower ICH score and lower initial hematoma volume. Study concluded that higher admission Mg levels were documented in patients with favorable functional outcome and functional independence at discharge. [24]

James E et al. investigated three hundred and thirteen patients who presented to their center within 48hrs of acute ischemic stroke. Serum Mg^{2+} was measured at the time of admission and at 24 hours after admission. Outcomes were compared among patients with low Mg^{2+} and patients with normal-to-high Mg^{2+}. Outcomes were further assessed according to whether their $Mg^{2+}$was lower at 24 hours than admission. Results showed that Mg^{2+} level was not predictive of poor functional outcome, death or discharge disposition and patients with decreasing serum Mg^{2+}did not have significant changes of neurologic deterioration or poor outcome compared to patients with unchanging or increasing Mg^{2+} levels. [34].

Cojocaru studied forty patients with acute ischemic stroke among them 26 women and 14 men, without any other serious injuries. Twenty-one healthy subjects, sex-and age-matched were selected as controls. The serum levels of Mg were checked on admission, and at 48 hours after the onset of ischemic stroke. Using NIHSS, the neurological deficit was assessed on the 1st day, and 48 hours later. The results confirm that there is a relationship between a low Mg concentration in serum at 48 hours after onset of ischemic stroke and the intensity of the neurological deficit. Severity of paresis degree was higher in the patients with low Mg levels. The serum Mg concentration has been suggested to possibly affect the neurologic state. A decrease in the serum Mg concentration indicated the severity of the injury. [9]

Wen-Harn Pan studied a randomized controlled trial comprising 291 discharged stroke patients with modified Rankin scale (mRS) <4. There were 3 arms: 1) regular salt (Na salt), 2) potassium-enriched salt (K salt), 3) potassium-and magnesium-enriched salt (K/Mg salt). The NIH Stroke Scale (NIHSS), Barthel Index (BI), and mRS were evaluated at discharge, at 3 month, and at 6 month. Result showed that after the 6-month of intervention, the proportion of patients with good neurologic performance increased in a greater magnitude in the K/Mg salt group than in the K salt group and the Na salt group, in that order. The K/Mg salt group had a significantly increased or of achieving good neurologic performance compared with the Na salt group. [35]

Sanne M DorhoutMees randomly assigned patients aged 18 years or older with an aneurysmal pattern of subarachnoid haemorrhage on brain imaging who were admitted to hospital within 4 days of haemorrhage, to receive intravenous magnesium sulphate, 64 mmol/day, or placebo. In this study 1204 patients were enrolled among them 606 patients were assigned to the magnesium group and 597 patients to the placebo. Result showed that 158 patients (26·2%) had poor outcome in the magnesium

group compared with 151 (25·3%) in the placebo group. So this study concluded that magnesium is not superior to placebo for reduction of poor outcome after aneurysmal subarachnoid haemorrhage. [36]

3.Methods

This study was a cross sectional study conducted in Department of Medicine of Dhaka Medical College Hospital, largest tertiary hospital in Bangladesh. Study was conducted from October 2018 to March 2019. Total 100 patients were included in the study through purposive sampling. Patients aged 18 years or more of both sexes who were admitted into the department within 48 hours of onset of stroke were included. Pregnant patients and patients taking diuretics or laxatives or known to be suffered from malignancy, malnutrition or malabsorption were excluded from the study. All the patients or their attendants (in unconscious patient) were counseled regarding the study and interviewed after taking informed written consent. Data were collected in a semi structured questionnaire.

Blood sample were sent for biochemical analysis as well as estimation of serum magnesium level in biochemistry lab of Bangabandhu Sheikh Mujib Medical University (BSMMU), which is a reliable institute to estimate the serum magnesium level in a cheaper cost. The value of serum magnesium level within 0.75 – 1.0 mmol/L (1.5-2.0 meq/L) was considered as normal. Diagnosis of stroke was made based on CT or MRI of the brain. Furthermore, outcome of the patient were assessed by Modified Rankin scale (0-6 score). Outcome assessments were done in single time at the day of 7 of occurrence of stroke. At day 7, research physician assessed the outcome of the patient directly in the hospital, or over telephone, if the patients were discharged during the period. For this reason, personal contact numbers were collected during interview. Formal ethical approval was taken from ERC of Dhaka Medical College (DMC). Following completion of the data collection, data analysis was done by SPSS 20.

4.Result

Among 100 patients included in this study, maximum and minimum ages were 75 years and 41 years respectively. Mean age was 60.46 (±10.14) years. Majority of the patients were aged between 61 to 70 years (48.0%).58.0% of the patients were male and 42.0% were female. The age of the male patients ranged from 41 to 75 years with the mean age of 59.09 (±11.12) years, while the age of the female patients ranged from 45 to 75 years with the mean age of 62.36 (±8.37) years. Most of the patients belonged to lower (35%) and lower-middle (30%) socio-economic class.48% patients were smoker.42% of total respondents had ischemic stroke, 40% had intracerebral haemorrhage and 18% had subarachnoid haemorrhage on CT scan of brain. Among the risk factors, hypertension (64%) and smoking (48%) were the most common risk factors.

32% patients had hypomagnesemia. Serum magnesium level was significantly lower ($p<0.001$) in ischemic stroke patients (1.55 ±0.34) in comparison to hemorrhagic stroke patients (1.96 ±0.41) and patients with SAH (1.80 ±0.27). The level was similar between hemorrhagic stroke and SAH. Frequency of hypomagnesemia was also significantly higher ($p<0.001$) among ischemic stroke patients (59.5%) in comparison to haemorrhagic stroke patients (12.5%) and SAH patients (11.1%).

Effect of serum magnesium level on short term outcome determined by **modified Rankin Score** (mRS) on discharge in different types of stroke was assessed. A score of 0 – 2 was considered good and 3 – 6 was considered bad outcome. In ischemic stroke with hypomagnesaemia, only 16.67% patients had good outcome and 42.86% patients had bad outcome. **P-value** is 0.018 which is significant. However, In intracerebral haemorrhageand SAH, hypomagnesaemia was not found to be significantly associated with short term outcome (P-value 0.16 and 0.18 respectively).

Table 1: Sociodemographic characteristics of the participants (n=100)

Characteristics	Frequency	%
Age category (years)		
41-50	22	22
51-60	26	26
61-70	48	48
71-80	4	4
Sex		
Male	58	58
Female	42	42
Occupation		
Housewife	31	31
Businessman	22	22
Service holder	21	21
Farmers	18	18
Others	8	8
Socio-economic status		
Lower class	35	35
Mower-middle class	30	30
Upper-middle class	24	24
Upper class	11	11
Smoking status		

Non-smoker	52	52
Smoker	48	48

Table 2: Risk factors of stroke of study population with frequency (n=100)

Risk Factors	Frequency	Percentage
Diabetes Mellitus	24	24.0 %
Hypertension	64	64.0 %
Smoking	48	48.0 %
Dyslipidaemia	22	22.0 %
Alcoholism	8	8.0 %
Family history of stroke	34	34.0%
Family history of IHD	21	21.0%

Table 3: Effect of serum magnesium level on short term outcome in different strokes. (n=100)

Stroke type	Short term Outcome (mRS)	Hypomagnesaemia n	Normal Magnesium n	P-value
Ischemic stroke (n=42)	Good (0-2)	7	11	**0.018**
	Bad (3-6)	18	6	
IntracerebralHaemorrhage (n=40)	Good (0-2)	3	10	**0.160**
	Bad (3-6)	2	25	
Subarachnoid Haemorrhage (n=18)	Good (0-2)	1	2	**0.180**
	Bad (3-6)	1	14	
The percentage within parentheses represents percentage among patients of corresponding the stroke subtype. P value was determined by Chi-square test				

5.Discussion

Total 100 patients with stroke were included in our study. In this study, out of 100 patients, the age of the patients ranged from 41 to 75 years with the mean age of 60.46 (± 10.14) years. The mean age of the patients was significantly higher in stroke patients, with majority (48%) respondents being in 61-70 years age group. In the study of *Hossain et al*, the mean age was 66.44 (±14.8) which was in terms of male 66.26 (±12.80) and in terms of female 66.20 (±17.90). [37]In a study of *Rahman et al* most of the stroke patients (69%) were between 51-70 years of age. [38]*Saha et al* also found stroke occurs most commonly in 59-70 years age group. [39]This study confirms that the incidence rises with age in both sexes.

In this study, 58% were male and 42% were female and ratio was 1.38: 1 which coincide with that of *Kaur et al* (1.17: 1) and *Hakim et al (*1.67: 1). [40, 41] Stroke is more prevalent in men than women and that is confirmed by many studies. Males are 1.25 times more likely to suffer strokes than females. [42]Men may be at a somewhat greater risk for stroke than women, but the difference is small. Women tend to live longer than men who die of other comorbidities; as a result, they often outnumber men in stroke prevalence figures. [43]

Regarding socio-economic status of study population, 35% patients are from lower class, 30% from lower middle class, 24% from upper-middle class, and rest 11% patients are from upper class family. In the study of *Ghayyure*tal found lower class respondents in 25.5% cases and middle class in 74.5% cases. [44]

On imaging, ischemic stroke is most commonly seen (42%) in our study population due to cerebral infarct, 40.0% showed intracerebral hematoma while 18.0% showed subarachnoid hemorrhage. These findings are consistent with *Miah et al* in Bangladesh where they found cerebral infarction 49.13%, intra-cerebral haemorrhage was 31.89% and subarachnoid hemorrhage found in 18.96%. [45]But this results differs with western study where cerebral infarction was 85%, intra cerebral hemorrhage 10% and subarachnoid hemorrhage 5% of cases. [46]

Among the risk factors, hypertension was present in 64% cases. It correlates with *Saha et al* (60% cases) and *Hossain et al (*63% cases) and *Siddiqui et al (*69% cases). [37, 47, 48]Diabetes mellitus was present in 24% cases. The Copenhagen stroke study has shown that in 1135 acute stroke patients, 233 (20%) were suffering from diabetes mellitus which is similar to our result. [49] This results also correlates with the study of *Hossain et al* (21%). [47]History of smoking was present in 48% case which correlates with many studies. *Yano et al* and *Donnan et al* found strong association between cigarette smoking and stroke. [50, 51]

Serum magnesium level was significantly lower in ischemic stroke patients in comparison to hemorrhagic stroke patients and patients with sub-arachnoid hemorrhage ($p<0.001$). The mean serum magnesium level of the present study is quite similar to a Bangladeshi study by *Hossain et al* which reported magnesium level in all 50 patients was 1.59 (±0.37) mg/dL and among 33 ischemic stroke patients was 1.47 (±0.32) mg/dL, 17 hemorrhagic stroke patients was 1.83 (±0.34) mg/dL. [37] In another study by *Kashyap et al* found the mean serum Mg level was 1.96 (±0.22) mg/dL. [52] But It is somehow differ from a North Indian study by *Kaur et al* which reported ischemic stroke (42 cases) mean serum magnesium 2.05 (±48) mg/dL, haemorrhagic stroke (8 cases) 2.19 (±48) mg/dL ($P>0.05$). Study by *Kaur et al* reviewed of 60 consecutive patients with an admission criteria of acute stroke. Serum magnesium level were low in patients who had acute stroke (mean 2.07±0.47 mg/dL, $P<0.001$) but not in the control group (mean 3.58±0.16 mg/dL). [40]

Our study signifies the thing that, hypomagnesaemia causes poorer short-term outcome in ischemic stroke. *Saberi et al* also found that higher serum magnesium level is accompanied by higher function and better prognosis after an ischemic stroke which endorses the findings of our study. [33]*Siegler et al* (2013) also assumed higher serum levels of magnesium may contribute to improved outcome following ischemic stroke, which possibly is related to vessel recanalization. [32] No significant difference was noted in outcome of patients with haemorrhagic stroke (ICH and SAH) in relation to serum magnesium level. Like our study, *Goyal et al* also found no significant association between serum Mg levels at 48 hours and outcome on discharge among hemorrhage stroke patients. [24]

6.Conclusion

In this study, it was observed that more than half of the ischemic stroke patients have lower level of serum magnesium. It is also common in hemorrhagic stroke and SAH but in a lesser proportion. Moreover, ischemic stroke patients have significantly lower level of serum magnesium than other type of stroke. And this lower level of magnesium in closely related to poor outcome of the acute ischemic stroke patients. However, further studies are required to reach a consensus.

7.Further Scope

This is a small sample sized single centered study; therefore the findings could not be inferred as a general statement. However, serum magnesium level can be screened routinely in acute stroke patients. Further multicentered large sample studies would be needed to find out any causal relationship and to recommend for any intervention.

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