Assessment of Magnesium Levels in Ischemic Cerebral Stroke Patients and Its Correlation with Severity of Neurological Disability – A Longitudinal Observational Study from Sri Amritsar, Punjab

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ABSTRACT

BACKGROUND

World Health Organization (WHO) clinically defines a stroke as 'the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin'. Hypo magnesia (ionized form) leads to neuromuscular hyperirritability, tremors, increased vascular resistance, coronary vasospasm and hypertension. Magnesium deficiency triggers vasoconstriction enhancing vascular endothelial injury and hence leads to atherosclerosis. In the present study, we wanted to evaluate serum magnesium levels in ischemic cerebral stroke patients and correlate its severity with the neurological disability using modified Rankin scale (mRS) and Canadian neurological scale.

METHODS

It was a longitudinal observational study, undertaken in the Department of Medicine in Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar from December 2018 to June 2020. 60 patients with acute ischemic cerebral stroke fulfilling the inclusion criteria were selected. 5 ml venous sample for serum magnesium level was taken within 24 hours and on day 5 of admission. Presence or absence of hypomagnesemia in patients after acute cerebral ischemic stroke was recorded during the hospital stay of patients, receiving standard management protocol of ischemic stroke. The correlation co-efficient of serum magnesium level with modified Rankin scale and Canadian neurological scale was calculated.

RESULTS

The mean age of patients was 61.6 ± 1.6 years, 42 (70 %) patients were male and 18 (30 %) were females and there was male preponderance. The mean serum magnesium level was measured as 1.78 ± 0.2 mg/dL, it was observed that the mean value for mRS was 3.93 ± 0.75 and Canadian neurological scale was 7.11 ± 2.01 within 24 hours and on the 5th day the mean value for mRS was 3.5 ± 1.09 and Canadian neurological scale was 8.02 ± 2.97. The present study observed a statistically significant correlation between mRS score and serum magnesium level as well as Canadian neurological scale and serum magnesium levels.

CONCLUSIONS

It was concluded through the results of this study that low levels of magnesium in the body can cause more severe stroke.

KEYWORDS

Stroke, Serum Magnesium, Hypomagnesemia, Modified Rankin Scale, Canadian Neurological Scale

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DOI: 10.18410/jebmh/2021/586

How to Cite This Article:
Kaur J, Nayyar SB, Sikri T, et al. Assessment of magnesium levels in ischemic cerebral stroke patients and its correlation with severity of neurological disability – a longitudinal observational study from Sri Amritsar, Punjab. J Evid Based Med Healthc 2021;8(35):3224-3229. DOI: 10.18410/jebmh/2021/586

Submission 12-02-2020,
Peer Review 20-12-2020,
Acceptance 07-08-2021,
Published 24-08-2021.

BACKGROUND

As per the WHO definition, stroke is a clinical syndrome defined as 'the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin'.[1]

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is the most widely used clinical outcome measure for stroke clinical trials. The scale runs from 0 - 6, running from perfect health without symptoms to death.[2]

Canadian neurological stroke scale provides a standardized neurological assessment of cognitive and motor function in stroke patients (alert or drowsy). It measures the deficit due to stroke. It includes the following assessments: Level of Consciousness, Orientation, Aphasia, Motor Strength.

Assessment of Motor Function is Separated into Two Sections:

A1 - administered if patient is able to understand and follow instructions.

A2 – administered in the presence of comprehension deficits.

Scores submitted from each domain section are summed to provide a total score out of a possible 11.5. Lower scores are representative of increasing severity.[3]

Magnesium (Mg^{2+}) plays a significant role in multiple biological systems and acts as a cofactor in hundreds of enzymatic reactions in the human body. The daily magnesium requirement for a human being is 200 - 300 mg. Low Mg level has been associated with increased risk of chronic diseases such as in cardiovascular disease (CVD), type 2 diabetes, metabolic related diseases, and colorectal cancer.[4]

Magnesium is a cation with essential roles in normal physiological function. Mg modulates vascular smooth muscle tone, peripheral vascular resistance, and blood flow dynamics. Mg also plays crucial roles in haemostasis by accelerating activation of factor X via factor VII–tissue factor, causing conformational changes in coagulation factor IX that augments its biological activities, potentiating platelet aggregation and decreasing levels of the intrinsic anti-thrombotic protein S and C.[5]

Hypomagnesaemia leads to neuromuscular hyperirritability, tremors, increases vascular resistance, coronary vasospasm and hypertension. Magnesium deficiency triggers vasoconstriction, enhances vascular endothelial injury and hence leads to atherosclerosis. Magnesium excess causes central nervous features associated uremia.[6]

In the brain, magnesium joins with adenosine triphosphate to form a complex which acts as a non-competitive N-methyl-D-aspartate (NMDA) receptor blocker. This complex inhibits the release of excitatory neurotransmitters at the presynaptic level and blocks voltage-gated calcium channels.[7]

Objectives

1. To evaluate the neurological status in acute ischemic cerebral stroke patients, using modified Rankin scale and Canadian neurological scale within 24 hours of admission and on day 5 of admission.
2. To estimate the serum magnesium levels in acute ischemic cerebral stroke patients on day 1 and on day 5 of admission.
3. To correlate the serum magnesium levels of acute ischemic cerebral stroke subjects with the neurological status of the patient using modified Rankin scale and Canadian neurological scale.

METHODS

The present study was conducted in Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar among the patients who satisfied the inclusion and exclusion criteria. 60 patients of acute ischemic cerebral stroke, diagnosed by history and magnetic resonance imaging (MRI) brain / computed tomography (CT) brain were taken for the study, after taking ethical clearance and written and informed consents from the patients and the guardian, if the patient was in debilitated state.

Inclusion Criteria

1. Diagnosis of acute ischemic cerebral stroke based on history, physical examination and MRI/CT of the brain.
2. Patient's admitted within 72 hours of stroke.
3. Age > 18 years.

Exclusion Criteria

1. Haemorrhagic infarct (diagnosed on history and MRI/CT of the brain)
2. Chronic kidney disease.
3. Alcoholic liver disease.
4. Thyroid disorders.
5. Patients on drugs that affect serum magnesium levels like diuretics, digoxin and antibiotics like amphotericin B, aminoglycosides.
6. Age < 18 years.

Data Collection

A detailed clinical history and clinical examination was done on participating subjects. Information of the study participants was noted using a pre-designed semi-structured study proforma. Demographic features (age and sex), family history, drug history, history of alcohol intake, smoking, height, weight, BMI (as per Asian guidelines) and medical history were noted. Diagnosis was confirmed by MRI/CT brain in acute ischemic cerebral stroke patients. 5 ml of venous blood was collected from all 60 subjects and serum

magnesium levels were collected on day 1 and day 5 of admission for the study. Presence or absence of hypomagnesemia in patients was recorded and the severity of neurological impairment was evaluated as per modified Rankin Scale and the Canadian neurological scale within 24 hours of admission and on day 5 of admission.

Statistical Analysis

The data was compiled in Microsoft Excel and analyzed in Statistical Package for Social Sciences (SPSS) version 23 (IBM, NY). The quantitative data were described as means and standard deviation, while qualitative data were described as frequency distribution and percentages. It was a longitudinal, observational study and the results obtained were statistically analysed. Univariate analysis was done with Pearson product and regression correlation coefficient where valid. A chi squared test was used to analyse the probability of differences in frequency distributions and $P < 0.05$ was taken to be statistically significant in all calculations.

RESULTS

The mean age of the patients was 61.6 ± 1.6 years. The maximum number of the patients were in the age group of 61 - 70 years constituting 18 (30.0 %) patients. In the present study, 42 (70 %) patients were males and 18 (30 %) were females and there was male preponderance. The mean systolic blood pressure was 151.46 ± 18.5 mmHg and the mean diastolic blood pressure was 95.73 ± 10.5 mmHg. 24 (40 %) patients gave history of diabetes mellitus and 36 (60 %) patients did not have a history of diabetes mellitus. 14 (23.3 %) patients gave prior history of smoking and 46 (76.7 %) patients had no prior history of smoking.

42 patients (70.0 %) presented with mild Glasgow coma scale (GCS), 16 patients (26.7 %) presented with moderate GCS and 2 patients (3.33 %) presented with severe GCS, within 24 hours of admission. On the 5th day, 45 patients (78.95 %) had mild GCS, 10 (17.55 %) had moderate GCS and 2 (3.50 %) had severe GCS.

The mean serum magnesium level, within 24 hours of admission was 1.78 ± 0.2 mg/dL. Serum magnesium levels were decreased in 37 (61.67 %), 21 (35.00 %) had normal serum magnesium levels and 2 (3.33 %) had increased serum magnesium levels. On the 5th day, the mean serum magnesium was 1.83±0.4 mg/dL. 22 (38.60 %) patients had decreased serum magnesium levels, 34 (59.65 %) had normal serum magnesium levels and 1 (1.75 %) had increased serum magnesium levels. The difference between mean serum magnesium levels within 24 hours and on 5th day was significant ($P = 0.02$).

The modified Rankin scale mean score within 24 hours was 3.93 ± 0.75 and on the 5th day was 3.36 ± 0.12. On association of serum magnesium levels with modified Rankin scale, within 24 hours of admission 81.0 % were in mRS 4 and 9.5 % were in mRS 5 with normal magnesium levels i.e., about 90 % patients were having moderately severe to severe disability which decreased on 5th day to 35.3 % having mRS 4 and 2.9 % in mRS 5, showing that as serum magnesium was back to normal levels on 5th day there was significant improvement in neurological disability. (within 24 hours: $R_s = 0.22$), (On 5th day: $R_s = -0.317$).

The mean Canadian neurological scale within 24 hours was 7.11 ± 2.01 and on the 5th day was 8.02 ± 2.97. On association of serum magnesium levels with Canadian neurological scale, within 24 hours of admission, 21 (35 %) patients were having normal serum magnesium levels and on the 5th day it increased to 34 (59.67 %) but there was no significant change in severity of Canadian neurological scale as 61.9 %, 33.3 % and 4.8 % within 24 hours and 55.8 %, 38.2 % and 5.9 % on 5th day were having mild, moderate and severe stroke respectively. 37 (61.67 %) were having decreased serum magnesium levels within 24 hours and on the 5th day it decreased to 22 (38.58 %) and the number of patients with mild severity stroke increased from 27 % within 24 hours to 59.1 % on 5th day. 2 (3.33 %) were having increased serum magnesium levels within 24 hours of admission and on the 5th day, 1 (1.75 %) was having increased serum magnesium level. Thus, more percentage of patients with decreased serum magnesium levels moved from severe and moderate grade to moderate and mild grade of Canadian neurological scale when serum magnesium levels became normal. (Within 24 hours: $R_s = 0.17$) (On 5th day: $R_s = 0.52$)

Age Group in Years	No.	%
≤ 40	4	6.7
41 - 50	14	23.2
51 - 60	10	16.7
61 - 70	18	30.0
71 - 80	10	16.7
➢ 80	4	6.7
Total	**60**	**100.0**
Mean ± SD in years	61.6 ±1.6	

Table 1. Distribution According to Age of Patients

Sex	No.	%
Female	18	30.0
Male	42	70.0
Total	**60**	**100.0**

Table 2. Distribution According to Gender of Patients

Magnesium Level	Within 24 hours		5th day	
	No.	%	No.	%
Normal (1.8 - 2.4 mg/dl)	21	35	34	59.65
Decreased (< 1.8 mg/dl)	37	61.67	22	38.60
Increased (> 2.4 mg/dl)	2	3.33	1	1.75
Total	**60**	**100**	**57**	**100**
Mean ± SD Mg^{2+}	1.78 ± 0.2		1.83 ± 0.4	
P value	0.02 (significant)			

Table 3. Distribution of Serum Mg^{2+} Level and Comparison of Mean Magnesium Levels within 24 Hours of Admission and 5th Day

Serum magnesium levels (mg/dL)		Modified Rankin Scale Within 24 hours Score				
		2	3	4	5	Total
1.8 - 2.4 (Normal)	N	0	2	17	2	21 (35.0 %)
	%	0.0	9.5	81.0	9.5	100.0
< 1.8 (Decreased)	N	1	13	12	11	3 (61.67 %)
	%	2.7	35.2	32.4	29.7	100.0
➢ 2.4 (Increased)	N	0	1	0	1	2 (3.33 %)
	%	0.0	50.0	0.0	50.0	100.0
Total	**N**	**1**	**16**	**29**	**14**	**60**
	%	**1.7**	**26.7**	**48.3**	**23.3**	**100.0**
Rs= 0.02; P-value: 0.867						

Table 4. Distribution of Serum Mg^{2+} Levels with Modified Rankin Scale within 24 Hours of Admission

Serum Magnesium Levels (mg/dL)		Modified Rankin Scale 5th day Score 1	2	3	4	5	Total
1.8 - 2.4 (Normal)	N	1	6	14	12	1	34 (59.67 %)
	%	2.9	17.7	41.2	35.3	2.9	100.0
< 1.8 (Decreased)	N	0	4	5	8	5	22 (38.58 %)
	%	0.0	18.2	22.7	36.4	22.7	100.0
➢ 2.4 (Increased)	N	0	0	0	1	0	1 (1.75 %)
	%	0.0	0.0	0.0	100.0	0.0	100.0
Total	**N**	**1**	**10**	**19**	**21**	**6**	**57**
	%	**1.8**	**17.5**	**33.3**	**36.9**	**10.5**	**100.0**

Table 5. Distribution of Serum Mg^{2+} Levels with Modified Rankin Scale at 5th Day of Admission

Serum Magnesium Levels (mg/dL)		Canadian Neurological Scale – Stroke Severity Within 24 Hours Score Mild	Mod	Severe	Total
1.8 - 2.4 (Normal)	N	13	7	1	21 (35.00 %)
	%	61.9	33.3	4.8	100.0
< 1.8 (Decreased)	N	10	22	5	37 (61.67 %)
	%	27.0	59.5	13.5	100.0
➢ 2.4 (Increased)	N	0	1	1	2 (3.33 %)
	%	0.0	50.0	50.0	100.0
Total	**N**	**23**	**30**	**7**	**60**
	%	**38.3**	**50.0**	**11.7**	**100.0**

Table 6. Distribution of Serum Mg^{2+} Levels with Canadian Neurological Scale within 24 Hours of Admission

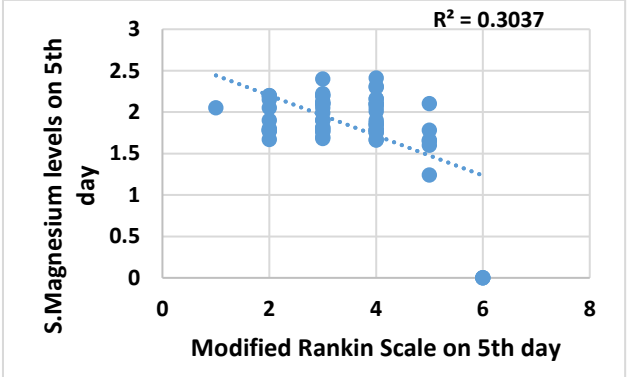

Figure 1. Correlation of MRS and S. Mg2+ Levels on 5th Day

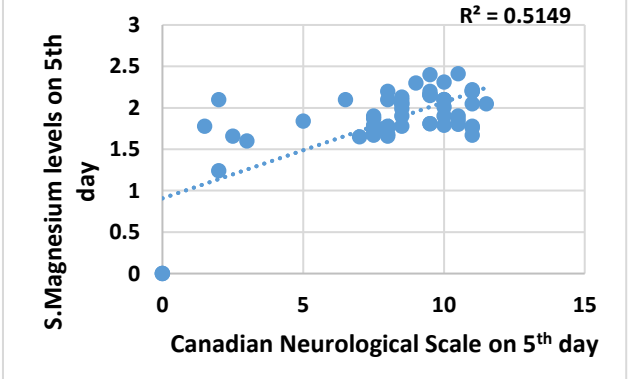

Figure 2. Correlation of Canadian Neurological Scale and S. Mg2+ Levels on 5th Day

Serum Magnesium Levels (mg/dL)		Canadian Neurological Scale – Stroke Severity 5th day Score Mild	Mod	Severe	Total
1.8 - 2.4 (Normal)	N	19	13	2	**34 (59.67 %)**
	%	55.9	38.2	5.9	**100.0**
< 1.8 (Decreased)	N	13	6	3	**22 (38.58 %)**
	%	59.1	27.3	13.6	**100.0**
➢ 2.4 (Increased)	N	0	0	1	**1 (1.75 %)**
	%	0.0	0.0	100.0	**100.0**
Total	**N**	**32**	**19**	**6**	**57**
	%	**56.2**	**33.3**	**10.5**	**100.0**

Table 7. Distribution of Serum Mg^{2+} Levels with Canadian Neurological Scale at 5th Day of Admission

DISCUSSION

In the study population, 30 % of the acute ischemic stroke cases were aged between 61 - 70 years, with mean age of 61.6 ± 1.6 years. Kotwal V et al. also observed that mean age of patients was 60.7 ± 11.7.[8]

In the present study, males were more affected by acute ischemic stroke. Khan M et al. in his study noticed there were 134 (67 %) males while 66 (33 %) were females.[9] The incidence of cerebrovascular accidents is more in males and elderly probably because most of the risk factors for stroke such as hypertension, dyslipidaemia, smoking etc, are present in males more frequently compared to females.

In this study, the prevalence of hypertension was 81.66 %. This result correlated with the findings by You S et al. (78 %)[10] and Paranthakan et al. (66 %).[11]

In this study, the mean serum magnesium level, within 24 hours of admission was 1.78 ± 0.2 mg/dL and on the 5th day was 1.83 ± 0.4 mg/dL. Similar results have been observed in other studies. According to a study by Cojocaru IM et al. in the year 2007, the mean serum magnesium level in patients suffering from acute ischemic stroke was 1.71 ± 0.51 mg/dL.[12] Patel RK et al. in his study observed that the level of serum magnesium is significantly lower in stroke patients when compared to the healthy subjects.[13]

In the present study, on association between serum magnesium levels and modified Rankin scale, within 24 hours of admission, there was no patient in mRS 0, mRS 1, mRS 2 but on 5th day when serum magnesium levels came to normal, 7 (20.6 %) patients were in modified Rankin score of 0 - 2 which is considered as good outcome with individuals assuming complete functional independence. Within 24 hours of admission, 9.5 % were in mRS 3 with normal serum magnesium levels but on 5th day it increased to 41.2 % in mRS 3, which is moderate disability. Within 24 hours of admission 81.0 % were in mRS 4 and 9.5 % were in mRS 5 with normal magnesium levels i.e., about 90 % patients were having moderately severe to severe disability which decreased on 5th day to 35.3 % having mRS 4 and 2.9 % in mRS 5, showing that as serum magnesium level was back to normal levels on 5th day there was significant improvement in neurological disability *(5th day, R_s= -0.317)*. In a similar study conducted by Shkirkova, K et al. 73 patients of acute ischemic stroke were included in the study and neurological assessment was done using modified Rankin scale. 1 (1.4 %) patient was in mRS 1, 23 (21.9 %) patients were in mRS 2, 23 (31.5 %) patients were in mRS 3, 20 (27.4 %) patients were in mRS 4 and13 (17.8 %) were in mRS 5. Serum magnesium levels were decreased in 63 patients. The P value was calculated which was 0.002. This showed that the deficiency of magnesium has poor neurological outcome in patients suffering from cerebrovascular accidents.[14] In a study conducted by Kotwal V et al. it was observed that serum magnesium was lower in the study group (mean of 1.85 ± 0.36) as compared to the control group (mean of 2.4 ± 0.21) which was statistically significant (P value = 0.001). Modified Rankin score was 4 to 5 in 27 patients and 2 to 3 in 23 patients and it was negatively correlated with serum magnesium levels (r = -0.67). It was found that serum

magnesium levels were lower in stroke patients than in controls and also within the stroke group patients with higher neurological disability had a lower score than patients with a lower neurological disability.[8]

In this study, it is noticed that both mRS and Canadian neurological scale can be used for the neurological assessment. In mRS, there is a six-point score, therefore, it is less probable to change than other stroke scales and the specificity of the scale is less. As for Canadian neurological scale, it has greater sensitivity and specificity even when the sample size is small. The present study observes a statistically significant correlation between mRS score and serum magnesium level as well as Canadian neurological scale and serum magnesium levels, which indicates that severity of a stroke is inversely related to the level of serum magnesium. The present study suggests that low serum magnesium levels in body is associated with more severe neurological deficits. Thus, serum magnesium may have a neuroprotective role and magnesium replacement in acute cerebral ischemic stroke patients with low serum magnesium levels may help in reducing neurological deficits.

CONCLUSIONS

1. In the present study done on 60 patients of ischemic cerebral stroke patients, the mean serum magnesium level, within 24 hours of admission was 1.78 ± 0.2 mg/dL and on the 5th day was 1.83 ± 0.4 mg/dL.
2. Patients with acute ischemic cerebral stroke with decreased serum magnesium levels were having more severe neurological deficit on mRS scale within 24 hours of admission and on 5th day when serum magnesium level was in normal range, there was decrease in severity of neurological deficit and patients improved and the relationship was statistically significant.
3. On assessment by Canadian neurological scale, severity of neurological deficit was less when serum magnesium level was in normal range on 5th day and the relationship was statistically significant.
4. The present study shows that low serum magnesium levels in body is associated with more severe neurological deficit and there was improvement in neurological deficit when serum magnesium was back to normal range. Thus, serum magnesium may have a neuroprotective role and magnesium replacement in acute cerebral ischemic stroke patients with low serum magnesium levels may help in reducing neurological deficit. Whether magnesium supplementation in acute cerebral stroke patients with normal serum magnesium levels has a role in neuroprotection, is a matter of further study.

Acknowledgement

The authors acknowledge the constant help and tremendous support provided by the Department of Medicine, SGRDIMSR, Sri Amritsar. We would also like to thank our Institute SGRDIMSR, Sri Amritsar for providing the necessary facilities to carry out this research.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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