Journal of Population Therapeutics & Clinical Pharmacology

EFFECT OF INTRAVENOUS MGSO4 REPLACEMENT ON FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Dr. Gullali[1*], Dr. Maryam Hussain[2], Dr. Wahaj Ul Hassan Khan[3], Dr. Ayesha Laraib[4], Dr. Amjad Khan[5], Dr. Naeem Ullah[6]

[1*]Trainee Medicine, CMH, Peshawar - Pakistan
[2]MBBS, FCPS Medicine and Pulmonology, Medical Specialist and Pulmonologist, CMH, Peshawar - Pakistan
[3] MBBS, FCPS Medicine and Neurology, Medical Specialist and Neurologist, CMH, Peshawar - Pakistan
[4]Demonstrator Anatomy Department, Ayub Medical College, Abbottabad - Pakistan
[5]Trainee Pulmonology, Fatima Jinnah Institute of Chest Diseases, Quetta - Pakistan
[6]Trainee Medicine, Khyber Teaching Hospital, Peshawar - Pakistan

[*]**Corresponding author:-** Dr. Gullali
*Email address: gulmalik125@gmail.com

ABSTRACT

Objective: To assess the efficacy of MgSO4 on functional outcome of patients presenting with acute ischemic stroke

Study Design: Quasi-experimental study

Place and Duration: Intensive Care unit, Tertiary Care Hospital Peshawar, April 2022- September 2022.

Methods: Patients of either gender between 45-80 years, presenting within 24 hours with clinical features and CT/MRI findings of acute ischemic stroke were included in the study. Non-probability consecutive sampling technique was employed and participants were placed in Group M (received MgSO4) and Group P (received placebo). Demographic characteristics, Mg levels, NIHSS scoring at admission, discharge and after 01 month were recorded parameters.

Results: Total 110 participants having male to female ratio of 2.2:1 with a median (IQR) age of 61.5years (57-65) were included. Hypertension was most common comorbidity in 55 patients (50%). Median (IQR) serum Mg levels at the time of admission were comparable among groups. After 48 hours of treatment, serum Mg levels were significantly greater in Group M as compared to Group P. Assessment of functional outcome by using NIHSS among groups at the time of discharge revealed significant improvement in patients who received Mg as compared to placebo (p-value 0.041). After a period of 01 month, functional outcome using NIHSS revealed median (IQR) score of 09 (8-10) in Group M as compared to 10 (8.6-12) in Group P (p - 0.004).

Conclusion: Intravenous MgSO4 improves functional outcome in acute ischemic stroke patients at discharge and at follow up after 30 days.

Keywords: Critical Care, Ischemic Stroke, Magnesium Sulfate

Introduction

Acute ischemic stroke is one of the most common cause of disability in the middle and low income countries carrying a high risk of mortality. The global projected incidence of ischemic stroke till the

year 2030 was predicted to be 89.3 per 100,000 people.[1] As per the definition of World health organization, Stroke is a syndrome characterized by deteriorating focal or global neurological clinical features persisting for more than 24 hours or leading to death with no probable cause other than a vascular origin.[2]

Stroke incidents in Pakistan are commonly observed in the early 60 years to late 70 years of age which places a great burden on the health care workers. As per the epidemiological statistics the incidence of stroke was 95 per 100,000 people per year in Pakistan however prevalence reported in Khyber Pakhtunkhwa province was 1.2% and the common risk factors leading to these cerebrovascular accidents were smoking, hypertension, diabetes sedentary life style and obesity.[3,4]

The increasing burden of stroke on the health care system of our country warrants urgent attention and therefore early multidisciplinary intervention, monitoring and critical care is required for better outcome of the patients. Acute ischemic stroke leads to insufficient circulation to the brain and persistent occlusion of the vascular supply can lead to neurological deficits carrying a high risk of morbidity and mortality. The aim is to restore the blood supply and prevent cellular dysfunction as a result of secondary brain injury by the use of latest modalities.[5] Several trials have been conducted including thrombolytic drug therapies and endovascular interventions following stroke but no pharmacological therapy to date is considered as gold standard.[6]

Serum Mg levels play a vital role in the prognosis of neurological pathology and low level of serum Mg have been associated with poor outcome.[7] The role of Mg as a vasodilator and neuroprotection is proven by its role in pre-eclampsia and eclampsia which maintains hemodynamic stability and prevents eclamptic fits.

Treatment of acute ischemic stroke includes supportive treatment however studies on the use of thrombolytic agents are scarce leading to gap in research. This study aims at assessing the efficacy of early administration of Mg Sulfate (MgSO4) by evaluation of the functional improvement using National institute of health Stroke Scale at different intervals. This study will help in refining treatment modalities for acute ischemic stroke and will serve as a guide for future research.

Methodology

After approval of the ethical committee of hospital ERC # 0067/24 dated 04 March 2022 the quasi-experimental study was conducted at a Tertiary Care Hospital, Peshawar from April 2022- September 2022.

The previous trial revealed that mean NIHSS score at the time of discharge from hospital was 9.15±5.77 in placebo group as compared to 6.69±5.46 after Mg administration.[8] Using a 90% power of study with level of significance as 5%, a sample size of n=110 was calculated with WHO sample size calculator. Non-probability consecutive sampling technique was employed and participants were divided equally with 55 patients each into Group M who received MgSO4 and Group P (placebo).

Inclusion criteria: Patients of either gender having age of 45-80 years presenting with clinical features and Computed tomography (CT) scan/Magnetic resonance imaging (MRI) findings of acute ischemic stroke presenting to intensive care unit within 24 hours of the incident were included in the study.

Exclusion criteria: Patients with age of less than 45 years, hypotension, bundle branch block, atrioventricular nodal block, pregnancy, respiratory failure, serum creatinine levels of >3mg/dl, neuromuscular disorders or diagnosed with any condition other than ischemic stroke were excluded from the study. Furthermore, patients with NIHSS of more than 25 were also excluded from study because of lack of severe disability and less chances of improvement. Patients with serum magnesium levels above reference range before starting treatment were also excluded.

Protocol of the study was explained to the participants before inclusion in the research. Total 110 participants presenting within 24 hours with clinical features of stroke underwent CT scan/ MRI as per the hospital protocol. Patients with CT scan/MRI findings suggestive of acute ischemic stroke

were included in the trial. On admission, baseline hemodynamic parameters including heart rate, non-invasive blood pressure, oxygen saturation and temperature were recorded followed by 12 lead electrocardiography and commencement of continuous monitoring in intensive care units. Supportive therapy was initiated to maintain hemodynamic parameters, normocarbia, normoxemia, normothermia, and fluid/electrolyte balance with the aim to maintain intracranial pressure and perfusion. Functional assessment was done using NIHS scale before administration of Mg or placebo and recorded. Interpretation of NIHS scale is shown in Table-I. Blood samples were collected under aseptic measures and baseline laboratory investigations were sent to laboratory. Employing non-probability consecutive sampling technique 55 patients received MgSO4 infusion 4 grams in 50 ml of normal saline over 30 mins followed by 16grams of MgSO4 in 100 ml over 24 hours. 55 patients from Group P received normal saline in the same volume as MgSo4 and serum Mg was recorded before and after the treatment. Hemodynamic parameters were recorded and deep tendon reflexes were assessed after every 15 mins interval then after 12 hours, 24 hours and 48 hours at the end of the infusion. Labs for serum Mg levels were repeated after 48 hours. At the time of discharge assessment of functional outcome was repeated using NIHSS scoring and recorded. Patients were prescribed treatment at the time of discharge and a follow up after 01 month was planned. After 01 month all patients were reassessed and functional outcome as evident from NIHSS scoring was recorded.

Data analysis was performed using statistical package for social sciences (SPSS) version 23. For qualitative variables frequencies and percentages were used for interpretation and chi square analysis was employed for analysis of significance. Distribution of data was assessed by using Shapiro-Wilk test. Median (Interquartile range) values were calculated for quantitative variables and non-parametric tests were used if the data was non-normally distributed. A p-value of <0.05 was considered as significant.

Results

The number of participants included in the study was 110 with equal distribution of 55 patients in Group M and 55 patients in Group P. Male participants were more as compared to females with a male to female ratio of 2.2:1 with a median (IQR) age of 62(58-64) years in Group M as compared to 60(54-65) years in Group P. Hypertension was the most common comorbidity among the patients reported in 55 (50%) of the patients. Baseline characteristics of the patients are shown in Table II. Median (IQR) serum Mg levels at the time of admission and before the treatment was 1.86mg/dl (1.6-2.0) in Group M as compared to 1.95mg/dl (1.7-2.1) in Group P. After 48 hours of treatment serum Mg levels were significantly greater in Group M as compared to Group P with a p-value of <0.001. Serum Mg levels are shown in Table III. Assessment of functional outcome by using NIHS scale among groups at the time of discharge revealed significant improvement in patients who received Mg as compared to placebo (p – 0.041). After a period of 01 month reassessment of functional outcome using NIHS scale revealed median (IQR) of 09 (8-10) in Group M as compared to 10 (8.6-12) in Group P with a significant p-value of 0.004. Functional outcome among groups are shown in Table IV.

Table-I: Interpretation of NIH Stroke Scale

NIHS scale Score	Interpretation
0	No symptoms of Stroke
5 - 15	Minor Stroke
16 - 20	Moderate to Severe Stroke
21 - 42	Severe Stroke

Table–II: Baseline Characteristics among groups (n=110)

Variables		Group M (n = 55)	Group P (n = 55)	p-value
Gender	Males	40 (72.7%)	36(65.5%)	

n(%)		Females		15(27.3%)	19(34.5%)	0.409
Age in years Median (IQR)				62(58-64)	60(54-65)	0.905
Comorbidities n(%)	Smoking	Yes		20(36.4%)	28(50.9%)	0.124
		No		35(63.6%)	27(49.1%)	
	Hypertension	Yes		28(50.9%)	27(49.1%)	0.849
		No		27(49.1%)	28(50.9%)	
	Diabetes	Yes		19(34.5%)	26(47.3%)	0.175
		No		36(65.5%)	29(52.7%)	

Table III: Serum Mg levels in mg/dl among groups (n=110)

Variables	Group M (n = 55) Median (IQR)	Group P (n = 55) Median (IQR)	p-value
Pretreatment Mg levels	1.86 (1.6-2.0)	1.95 (1.7-2.1)	0.253
Post Treatment Mg Levels	4.28 (3.9-4.5)	1.96(1.8-2.2)	<0.001

Table–IV: Efficacy of MgSO4 versus Placebo among groups (n=110)

Variables	Group M (n = 55) Median (IQR)	Group P (n = 55) Median (IQR)	0.848
NIHS score at admission	30 (27-35)	29 (26-34)	0.848
NIHS score at discharge	18 (16-19)	19(18-21)	0.041
NIHS score after 01 month	09 (8-10)	10 (8.6-12)	0.004

Discussion

The quasi experimental study was conducted to assess the effectivity of intravenous MgSO4 versus placebo in patients presenting with acute ischemic stroke. NIHS scale was used to assess the functional outcome in all the patients included in the study. Our study revealed that after administration of intravenous Mg assessment of functional outcome at the time of discharge was significantly improved in 55 patients with median NIHS scale score of 18 (16-19) as compared to 55 patients in Group P with median NIHS scale score of 19(18-21). All the participants were reassessed after a period of one month and efficacy of MgSO4 was evident as revealed by significant improvement of NIHS scale score in Group M as compared to Group P. Similar to our study another randomized controlled trial revealed similar beneficial effects after Mg therapy in patients with acute ischemic stroke. Comparison of mean NIHS scale scores in patients who received Mg was 3.16±0.98 as compared to 1.84±1.06 in placebo group with a p-value of <0.01.[10] Wide range of effects posed by Mg and several trials confirm its neuroprotective role and its safety and tolerability in myocardial infarction.[11,12] Panahi Y et al conducted a randomized controlled trial and results concluded that patients of stroke who received amiodarone plus Mg had reduced disability following stroke with improvement in inflammatory, immunological and neurological indicators.[13]

Median age in our patients was 62 years in Group M as compared to 60 years in Group P and the most common comorbidity was hypertension followed by diabetes. We found that smoking was a common factor in most of our patients presenting with acute ischemic stroke. Similar to our results old age and hypertension were found to be the risk factors predisposing to stroke.[14]

The increase in the incidence of stroke worldwide makes it a center of attention. For a long period of time the treatment of stoke was confined to supportive therapy and use of antiplatelet drugs. Advances in the field of medicine have led to multiple trials to assess the role of thrombolytic and endovascular therapies.[15] Randomized controlled trials for the role of Mg in acute ischemic stroke are lacking and a few trials conducted to assess the role of Mg are not promising or conclusive

revealing no beneficial effect on focal/global neurological outcome and mortality at 90 days.[16] The paradox in the conclusion of Mg trials as evident by a systemic review revealed that after administration of Mg in 02 trials out of 04 trials there was improvement in disability and dysfunction assessment by using NIHS scale and Modified Rankin Scale. In the same review minocycline was found more effective in multiple conducted trials with a propensity of neuroprotective role after ischemic stroke.[17]

The multidisciplinary approach required for the treatment of acute ischemic stroke includes frequent assessment of the patient due to the vulnerability of post stroke complications. In our study after administration of MgSO4 serum Mg levels were significantly improved in Group M as compared to Group P ($p < 0.001$) Serum levels of Mg profoundly affect the conversion of ischemic stroke to hemorrhagic stroke. In a study conducted by Cheng Z et al it was found that 17% of the patients who presented with ischemic stroke had a complication of hemorrhagic stroke. Mean Serum Mg levels in these patients were significantly lower in these patients 0.81 ± 0.08 versus 0.85 ± 0.08 mmol/L in patients who did not develop hemorrhagic stroke.[18]

The beneficial role of Mg by providing neuroprotection and vasodilation of the cerebral vasculature to maintain a constant cerebral blood flow has been proven by multiple trials.[19]Increasing burdens of acute ischemic stroke patients in our country and the lacking trials on Mg therapy warrants specific attention. This quasi experimental trial can serve as a guide to perform randomized controlled trials in the future and proposal of definitive and cost effective treatment to patients presenting with acute ischemic stroke.

Conclusion
Intravenous MgSO4 improves the functional outcome in acute ischemic stroke patients at the time of discharge and at follow up after 30 days.

Limitations of the Study: The study was conducted at a single center with small sample size. All the participants were from the same region and ethnicity and the period of follow up was limited to 30 days.

Conflict of Interest: None

References:
1. Pu L, Wang L, Zhang R, Zhao T, Jiang Y, Han L. Projected global trends in ischemic stroke incidence, deaths and disability-adjusted life years from 2020 to 2030. Stroke. 2023 May;54(5):1330-9..DOI:10.1161/STROKEAHA.122.040073
2. Chugh C. Acute ischemic stroke: management approach. Indian J. Crit. Care Med. 2019 Jun;23(Suppl 2):S140. DOI: 10.5005/jp-journals-10071-23192
3. Khan MI, Khan JI, Ahmed SI, Ali S. Epidemiology of Stroke in A Developing Country [Pakistan]. LAP LAMBERT Academic Publishing; 2019 Jan.
4. Sherin A, Ul-Haq Z, Fazid S, Shah BH, Khattak MI, Nabi F. Prevalence of stroke in Pakistan: Findings from Khyber Pakhtunkhwa integrated population health survey (KP-IPHS) 2016-17. Pak. J. Med. Sci. 2020 Nov;36(7):1435..DOI: 10.12669/pjms.36.7.2824
5. Herpich F, Rincon F. Management of acute ischemic stroke. Crit. Care Med. 2020 Nov 1;48(11):1654-63. DOI: 10.1097/CCM.0000000000004597
6. Hasan TF, Hasan H, Kelley RE. Overview of acute ischemic stroke evaluation and management. J. Biomed. 2021 Oct 16;9(10):1486. DOI: 10.3390/biomedicines9101486
7. Goenka L, Satyanarayana CR, George M. Neuroprotective agents in acute ischemic stroke—a reality check. Biomed. Pharmacother. 2019 Jan 1;109:2539-47. DOI: 10.1016/j.biopha.2018.11.041

8. Sullivan M, Cunningham K, Angras K, Mackeen AD. Duration of postpartum Mg sulfate for seizure prophylaxis in women with preeclampsia: a systematic review and meta-analysis. J. Matern. -Fetal Neonatal Med. 2022 Dec 12;35(25):7188-93. DOI: 10.1080/14767058.2021.1946505

9. Afshari D, Moradian N, Rezaei M. Evaluation of the intravenous Mg sulfate effect in clinical improvement of patients with acute ischemic stroke. Clin Neurol Neurosurg. 2013;115:400–04. DOI: 10.1016/j.clineuro.2012.06.001

10. MOUSAVI S.A., ZIAEE J., SAADATNIA M.. MG SULFATE IN ACUTE STROKE: A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL. J Res Med Sci (JRMS) 2004;9(4):7-10.

11. Muir KW. Mg for neuroprotection in ischaemic stroke: rationale for use and evidence of effectiveness. CNS drugs. 2001 Dec;15:921-30. Doi: 10.2165/00023210-200115120-00002.

12. Botturi A, Ciappolino V, Delvecchio G, Boscutti A, Viscardi B, Brambilla P. The role and the effect of Mg in mental disorders: a systematic review. J. Nutr. 2020 Jun 3;12(6):1661. Doi:10.3390/nu12061661

13. Panahi Y, Mojtahedzadeh M, Najafi A, Gheini M, Abdollahi M, Sharifzadeh M et al. Protective Effects of Intravenous Mg Sulfate in Stroke Patients Receiving Amiodarone: A Randomized Controlled Trial. Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health. 2021:579-88.

14. Murphy SJ, Werring DJ. Stroke: causes and clinical features. J. Med. 2020 Sep 1;48(9):561-6. Doi:10.1016/j.mpmed.2020.06.002

15. Hollist M, Morgan L, Cabatbat R, Au K, Kirmani MF, Kirmani BF. Acute stroke management: overview and recent updates. Aging Dis. 2021 Jul;12(4):1000. Doi: 10.14336/AD.2021.0311

16. Avgerinos KI, Chatzisotiriou A, Haidich AB, Tsapas A, Lioutas VA. Intravenous Mg Sulfate in Acute Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J. Stroke Med. 2019 Apr;50(4):931-8. Doi:10.1161/STROKEAHA.118.021916

17. Ortiz JF, Ruxmohan S, Saxena A, Cox ÁM, Bashir F, Tambo W, Ghani MR, Moya G, Córdova I. Minocycline and Mg as neuroprotective agents for ischemic stroke: a systematic review. Cureus. 2020 Dec 28;12(12). DOI: 10.7759/cureus.12339

18. Cheng Z, Huang X, Muse FM, Lin X, Cao Y. Low serum Mg levels are associated with hemorrhagic transformation after thrombolysis in acute ischemic stroke. Front Neurol. 2020 Sep 2;11:567644. Doi: /10.3389/fneur.2020.00962

19. Pascoal AC, Katz L, Pinto MH, Santos CA, Braga LC, Maia SB, Amorim MM. Serum Mg levels during Mg sulfate infusion at 1 gram/hour versus 2 grams/hour as a maintenance dose to prevent eclampsia in women with severe preeclampsia: A randomized clinical trial. J. Med. 2019 Aug 1;98(32):e16779. DOI: 10.1097/MD.0000000000016779