




Effect of Serum Ionic Magnesium on Neurological Outcome in Severe Traumatic Brain Injury Patients: A Prospective Study

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Abstract

Background Magnesium is considered to have important role in cytotoxic and reperfusion pathways, deficiency of which may lead to secondary brain injuries; thus, hypomagnesemia is thought to be detrimental in traumatic brain injury (TBI) patients. The aim of this study was to evaluate the relationship between serum ionic magnesium level and neurological outcome in severe TBI patients.

Materials and Methods Eighty-four patients with severe TBI aged between 20 and 80 years admitted within 24 hours of injury included in our study. All patients were divided into two categories on the basis of initial serum magnesium levels as low serum magnesium level and normal serum magnesium level. Data was collected on the basis of age, gender, Glasgow Coma Scale (GCS) at the time of admission, and neurological outcome evaluation done on the basis of Glasgow Outcome Scale (GOS) at the end of 6 months.

Results Among the total patients, 32 patients had low serum magnesium level (< 1.6 mg/dL) at the time of admission. About 87.5% patients with low serum magnesium level had poor neurological outcome as compared to 12.5% of patients ($p < 0.001$) had good neurological outcome evaluated on the basis of GOS. Logistic regression model identified low Mg level (odds ratio = 6.593, $p = 0.002$) and GCS score less than 5 (odds ratio = 3.099, $p = 0.028$) as independent predictors of TBI.

Conclusion Hypomagnesemia seems to be an independent prognostic marker in severe TBI that can lead to poorer outcomes.

Keywords

- ▶ traumatic brain injury
- ▶ Glasgow Coma Score
- ▶ Glasgow Outcome Scale
- ▶ trauma
- ▶ magnesium

Introduction

Traumatic brain injury (TBI) is a common and complex injury caused by a sudden trauma to the brain or by an object piercing the brain tissue.¹ Outcome prediction after head injury is very difficult and also uncertain, hence very appropriately described in Hippocratic maxim as “no head injury is too severe to despair of, nor too trivial to ignore.”²

TBI is the leading cause of mortality and long-term disability hence termed as “silent epidemic.” The common indicators of severity of TBI include Glasgow Coma Scale (GCS) scores,³ duration of impaired consciousness and posttraumatic amnesia,⁴ presence of nonreactive pupils,⁵ and brain imaging techniques.⁶ Out of these most commonly used is GCS.

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Primary injury is caused by physical trauma to the brain, which causes nearby tissues to be compressed and sheared and may or may not cause loss of consciousness. The complex process known as secondary injury, which includes cranial and systemic sequelae, takes place in the hours and days after primary injury. The following are the examples of cranial complications: vasospasm, intracranial hypertension, cerebral edema, calcium ion toxicity, etc. Systemic complications include hypoxemia, hypotension, hypertension, hyperglycemia, hypoglycemia, and hypomagnesemia. Out of these serum magnesium level has been shown to be critical predictor of outcome of head injury. Magnesium plays an important role in cytotoxic and reperfusion pathways that leads to secondary brain injury.^{7,8} Hypomagnesemia can lead to very deleterious effect on central nervous system by various mechanism like vasoconstriction, platelet aggregation, free radical formation, and neuronal cell death by influx of calcium through calcium channel in N-methyl-D-aspartate (NMDA) receptor.⁹

This study was conducted with the aim to evaluate the relationship of serum level of ionic magnesium with neurological outcome among the patients of severe TBI.

Materials and Methods

Sampling

After obtaining institutional ethical committee approval (Ref. No.: 387 MC/EC/2022; Date: 09/05/2022), this prospective study was conducted in patients who got admitted in our center from June 2021 to May 2022.

The patients were enrolled for study after obtaining an informed and written consent. The sample size calculation was done in G*Power 3.1.9.2 software and considering 90% power, 5% alpha error, and 10% beta error, the total sample size was calculated as 78. A total of 84 patients were included in study. Out of which, 67 patients were operated and 17 patients were managed conservatively. Out of 67 operative patients, 61 patients were primarily operated and only 6 patients were operated in subsequent period. Patients with following characteristics were included aged more than 18 years and less than 80 years, admitted within 24 hours of injury, and post-resuscitative GCS score less than or equal to 8. Patients were excluded if they were found with any of the following features: TBI older than 24 hours, compound fracture, multisystem trauma, lacerated organs like liver, spleen, great vessels, lesions in the brainstem as an isolated finding, hypovolemic shock of grade III to IV, previous treatment, alcoholism, pregnancy, hypocalcemia, hypoalbuminemia, hypotension,

previous disabilities due to TBI, bilateral absent pupillary light reflex, and patients who had chances to lose to follow-up.

Methodology

Once the patients were stabilized, beside demographic and clinical features, blood samples were taken following admission. All patients were treated according to the Brain Trauma Guidelines, 4th edition.¹⁰ Blood sample was collected to evaluate the serum magnesium within 24 hours of admission. Based on the serum magnesium levels, the patients were divided into two groups: (a) low serum magnesium group with level below 1.6 mEq, and (b) normal group with serum magnesium of 1.6 to 2.5 mEq.¹¹ Glasgow Outcome Scale (GOS) was used for the assessment of outcomes at 6 months.

Statistical Analysis

Data tabulation and analysis were done using Microsoft excel and SPSS v.20 software, respectively. Continuous data was expressed as mean and standard deviation and compared with Student's t-test. Categorical data was compared with chi-square test. Multivariate analysis was conducted with logistic regression. Significance level was kept at *p*-value less than 0.05.

Results

The mean age of the participants was 50.46 years with a standard deviation of 15.7333 years (50.46 ± 15.73 years) ranging from minimum age of 18 years to maximum age of 80 years. There were 25 females and 59 males in the study. The median GCS at the time of admission was 5. The minimum GCS was 3 and maximum was 8. The mean serum magnesium content was 1.560 ± 0.42 mEq/L. The minimum was 1.0 mEq/L and maximum was 2.6 mEq/L.

Although both mean age and mean GCS score are greater in patients with normal magnesium levels, there was not significant difference ($p = 0.923$ and $p = 0.453$, respectively; ►Table 1).

Majority of the subjects having lower magnesium levels had poorer outcome in GOS. Statistically significant association was found between these variables ($p < 0.001$; ►Table 2).

Logistic regression model gives insights that lower magnesium levels have 6.593 times odds of having poorer outcomes ($p = 0.002$), while GCS less than 5¹² in the initial presentation has 3.099 times more odds of having poorer outcomes ($p = 0.028$); patients aged more than 40 years, however, had

Table 1 Comparison of age and GCS scores between low and normal Mg levels

Parameters	Mg levels	<i>n</i>	Mean	SD	SE mean	<i>t</i> -test	<i>p</i> -Value
Age (y)	Low Mg	32	50.25	16.070	2.841	0.097	0.923
	Normal Mg	52	50.60	15.678	2.174		
GCS score	Low Mg	32	5.25	1.503	0.266	0.754	0.453
	Normal Mg	52	5.52	1.639	0.227		

Abbreviations: GCS, Glasgow Coma Scale; Mg, magnesium; SD, standard deviation; SE, standard error.

Table 2 Comparison of GOS scores between low and normal Mg levels

Mg levels	GOS		Chi-square test	p-Value
	Good	Poor		
Low Mg	4	28	11.092	< 0.001
Normal Mg	25	27		

Abbreviations: GOS, Glasgow Outcome Scale; Mg, magnesium.

Table 3 Logistic regression model to evaluate various risk factors for poorer outcomes

Parameters	B	SE	Wald	df	Sig.	Exp (B)
Sex	-0.046	0.577	0.006	1	0.937	0.955
Age > 40 years	0.357	0.578	0.381	1	0.537	1.429
Low Mg	1.886	0.620	9.254	1	0.002	6.593
GCS < 5	1.131	0.516	4.814	1	0.028	3.099
Constant	-6.089	1.756	12.026	1	0.001	0.002

Abbreviations: GCS, Glasgow Coma Scale; Mg, magnesium; SE, standard error.

1.429 times more odds of having poorer outcome; however, this was not significant ($p = 0.537$; ► **Table 3**).

Discussion

With significant consequences in the cytotoxic and reperfusion pathways of secondary brain damage, magnesium is regarded as a key diagnostic measure of neurotrauma.¹³ Numerous investigations demonstrate that the total tissue and intracellular magnesium levels of the brain or spinal cord are significantly decreased after trauma,¹⁴ and that magnesium supplementation has an impact on the severity of posttraumatic cellular damage.^{13,15} The neurometabolic cascade following brain damage was thoroughly examined, and it was found that intracellular magnesium levels fall right away after TBI and stay low for up to 4 days. Since both glycolytic and oxidative ATP synthesis are hindered when magnesium levels are below normal, hypomagnesemia may result in neural dysfunction.¹⁶ Low magnesium levels also make it easier for the NMDA receptor channel to unblock, which increases the calcium ion influx and has been proven to damage neurofilaments and microtubules, affecting post-traumatic brain connections. It is never a good idea to have more calcium than magnesium in brain neurons because too much calcium stimulates neurons nonstop, which eventually results in cell death.¹⁵

Magnesium is essential for a number of physiological processes, including the release of neurotransmitters, protein synthesis, intracellular calcium control, energy and protein metabolism, and the coagulation cascade.^{17,18} However, a patient's prognosis may have an impact by an abnormal serum magnesium level.^{19,20} Hypomagnesemia has been linked to a poor outcome in several neurointensive patients, including ischemic stroke and intracerebral hemorrhage, according to some research.^{21–25} Regarding TBI patients, several studies show that hypomagnesemia occurs, with

an incidence ranging from 42.7 to 66%. However, the definition of hypomagnesemia used in these studies is inconsistent, and there is no consensus regarding the relationship between hypomagnesemia and the prognosis of TBI patients.^{26–28}

This study showed that subjects with lower magnesium levels had poorer outcome as assessed by GOS. Logistic regression model identified low Mg level (odds ratio = 6.593) and GCS score less than 5 (odds ratio = 3.099) as independent predictors of TBI. These findings are similar to the results of the study by Nayak et al²⁹ who reported that 81% of the patients with poor outcome had lower levels of serum magnesium ($p = 0.01$) and low serum magnesium was significantly associated with poor outcome ($p = 0.04$). Stippler et al³⁰ conducted a similar study and found that patients with low initial serum magnesium level were at 2.37 times greater risk for poor outcome ($p = 0.016$).

Since trauma-induced reductions in brain magnesium level have been linked to neurological and motor impairment, restoring magnesium homeostasis has become a focus of therapeutic approaches. Numerous studies have shown that giving magnesium chloride or magnesium sulphate before or after a traumatic event can improve neurological and cognitive outcomes in different experimental TBI models by restoring brain free magnesium levels, reducing brain oedema, and thus reducing the risk of brain injury.^{31,32}

Conclusion

This study has found the relationship between neurological outcomes of TBI with the serum magnesium concentration. Hypomagnesemia appears to be an independent prognostic marker in severe TBI patients that can lead to poor outcomes. Future multicenter experimental studies with larger sample size and with prospective design are recommended to explore potential therapeutic implications of magnesium in TBI patients with lower admission magnesium levels.

Conflict of Interest

None declared.

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