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Magnesium Sulphateas Neuroprotective in Post Traumatic Brain Injury

OSAMA M. ABDELWAHAB, M.D.*; HOSSAM M. KORANY, M.Sc.*; OMAR M. EL FALAKY, M.D.** and SAFINAZ H. OTHMAN, M.D.***

The Department of Neurosurgery, Faculties of Medicine, Beni-Suef and Cairo** Universities and Anesthesia, ICU & Pain Therapy Department***, Cairo University*

Abstract

Background: Many animal studies have delineated the neuroprotective effect of magnesium (Mg) in traumatic brain injuries. It protects neurons from ischemic injuries and supports neuronal survival following TBI.

Aim of Study: The aim of this study is to assess the role of Mg as a neuroprotective in patients with moderate and severe traumatic brain injury.

Patients and Methods: This is a double blind placebo controlled study. Sixty victims of traumatic brain injury (TBI), moderate and severe were randomly allocated into one of two equal groups; Mg sulphate (Group A), or normal saline as placebo (Group B) from April to August 2019 in one of neurosurgical ICUs in the following centers; Kasr El-Aini Hospitals, Beni-Suef University Hospital or Beni-Suef General Hospital. All patients had received the standard management as per brain trauma foundation guidelines, including surgical intervention when deemed necessary. Outcome was assessed using Glasgow outcome scale (GOS) and mortality rate after two months.

Results: From April to August 2019, sixty victims of TBI has been enrolled. Patients have been admitted to neurosurgical intensive care unit. The mean age was 33.9 years. Sex distribution showed an evident male predominance in both groups (83.3%). After 2 months, favorable outcome (good recovery and moderate disability) was achieved in 18 patients in group A, and 19 patients in group B, the difference was statistically insignificant. There were 22 mortality that represented 36.6% of the whole study group, 12 cases in group A, and 10 cases in group B.

Conclusion: The study did not identify a significant beneficial effect in reducing mortality in traumatic brain injury after administration of Mgso4; however, it suggested that magnesium sulfate shows a tendency to improve the outcome after 2 months as long as GCS was better on admission.

Correspondence to: Dr. Osama M. Abdelwahab,
The Department of Neurosurgery, Faculty of Medicine,
Beni-Suef University

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Key Words: *TBI – Neuroprotection – Magnesium sulfate – GOS.*

Introduction

TRAUMATIC brain injury (TBI) is the main cause of death and disability more than any other traumatic insult. It is a public health problem with high impact in both developed and developing countries **[1].** Mechanism of injury can be divided into primary and secondary. Primary injury due to tissue destruction appears immediately after the blow, in the form of contusions, hematomas, or diffuse axonal injury. Secondary injury consists of multiple pathological biochemical cascades that occur within minutes to days of the primary injury in the form of free-radical generation, depolarization, excitotoxicity, and disruption of blood brain barrier (BBB) **[2,3,4].** In other words, the negative effects in secondary injury could be preventable, making it the primary therapeutic target in neurocritical care patients.

List of Abbreviations:

TBI	: Traumatic brain injury.
GOS	: Glasgow outcome scale.
BBB	: Blood brain barrier.
NMDA	: N-methyl-D-aspartate.
CP	: Cerebral palsy.
GCS	: Glasgow coma scale.
ICU	: Intensive care unit.
RTA	: Road traffic accident.
CT	: Computerized tomography.
SD	: Standard deviation.
CSF	: Cerebrospinal fluid.

The neuroprotective mechanism of magnesium could be attributed to NAMDA (N-methyl-D-aspartate) channels blocking, inhibition of presynaptic excitatory neurotransmitters, inhibition of voltage-gated calcium channels, potentiation of presynaptic adenosine, and relaxing effect on vascular smooth muscles with secondary increase in cerebral blood flow [5]. Neuroprotective effect of magnesium has been well established in many experimental studies of TBI inrats [6,7,8,9].

In humans, the inhibitory effect of magnesium underpinned its utilization as an anticonvulsant especially in eclamptic seizures [10]. In preterm neonates, antenatal administration demonstrated preventive effect against CP (cerebral palsy) [11]. Urinary loss of magnesium, and hypomangnesimia has been reported in humans after TBI, with results linked to poor prognosis [12,13].

In order to translate the putative neuroprotective effect of magnesium in TBI, we organized a multi-center, double-blind, randomized, placebo-controlled, Phase III clinical trial (Mgso4 as Neuroprotective in Post Traumatic Brain Injury).

Patients and Methods

Sixty subjects with post traumatic brain injury either moderate (GCS = 9-12) or severe (GCS = 3-8) will be randomly allocated into two equal groups; Group (A) will receive MgSo4 within 24 hrs of trauma, and Group (B) will receive normalsaline as a placebo. Patients will be admitted in one of the neurosurgical ICUs in the following centers; Kasr El-Aini Hospitals, Beni-Suef University Hospital or Beni-Suef General Hospital from April to August 2019. Each patient will receive all other standard management as indicated on individual basis and as per brain trauma foundation guidelines, [14] (e.g. Antiepileptics, brain dehydrating measures, antibiotics, ventilatory support, or surgical intervention when indicated).

Inclusion criteria:

1- Patients with moderate (GCS = 9-12), or severe (GCS = 3-8) traumatic brain injury.
2- Patients presented and admitted within 24 hrs oftrauma.
3- Age above 12 years.
4- Written informed consent form the patient's next of kin.

Exclusion criteria:

1- Non consentingpatients.
2- Persistent hypotension (BP below 90 / 60) in 1st 24 hours despite measures of resuscitation.
3- Significant multisystem association (e.g. cord injury with spinalshock).
4- Known case of renalfailure.

For each patient, the following will be recorded:

1- Personal data: Name, age, sex, address, contact no.
2- Mode of trauma: Fall from height, RTA (road traffic accident), or isolated head trauma.
3- Neurological assessment on admission using the Glasgow coma score.
4- Associated injuries or neurological deficits.
5- Findings of initial CT brain, as well as follow-up scans.
6- Any previous illness.

Administration and safety:

Initial dose: Within 24 hrs of trauma; 50mg/kg/ IV infusion over 1 hour. Maintenance dose: 25mg/ kg twice daily for 48 hrs.

In order to avoid possible Mgso4 toxicity, infusion of the medication (either Mgso4 or placebo) will be abruptly terminated whenever:

a- Urine output <0.5ml/kg/hour over 4 hours.
b- Blood urea >50mg/dL.
c- Fall of systolic BP <90mmHg.
d- Respiratory center depression (respiratory rate less than 12 perminute).
e- Cardiac arrhythmia.
f- Loss of deep tendonreflexes.

The fourth author will be responsible for setting, implementing and monitoring the safety measures during the study.

Drug preparation and blinding:

The medication will be prepared by three volunteers other than the researchers, one in each center where the study will be conducted.

For each patient, a set of bottles will be prepared (initial dose, and 4 maintenance doses). After preparation, each set of bottles will be labeled using the same code consisting of letters (A, B, C, D, E, F) and figures (0 to 9). Total number of codes will be 60 which is the total number of patients allocated (A0, A1, A2,....A9 & B0, B1, ... B9 & C1,...C9 & D0-D9 & E0-E9 & F0-F9).

Each amp of Mgso4 (0.5gm/5ml) will be dissolved in 13.5ml normal saline (at that concentration, Mgso4 remains chemically stable for 3 days in room air).

For simplicity, this composes a unit and will be labeled as previously mentioned, so one unit equals 500mg dissolved in 18.5ml normal saline. For each patient, the number of units will be calculated according to the body weight. For example, the initial dose or the daily dose of 70kg patient equals 7 units (70 x 50 = 3500mg). For this patient, 3 bottles will be prepared on admission, each bottle labeled the same as the units, and each bottle contained 7 units.

The first bottle will be given as the initial dose, and the other two bottles will be divided into 4 equal doses, and to be given over the next 48 hrs. For placebo, the same will be done, but only using normal saline, which is identical to Mgso4 regarding color and aspect.

Only the third author will be acquainted with the key of the code, either it is the studied treatment (Mg So4), or normal saline (placebo). He will be responsible for the random allocation of the patients, and to instruct the volunteers to prepare either the treatment or the placebo, and their subsequent coding. He is totally blind regarding the results which will be regularly recorded. The key will be kept hidden from all other researchers. The key will be disclosed only after conclusion of the study and collection of the results in order to operate the statistical analysis.

Follow-up:

Patients will be regularly monitored with GCS recorded at day three and day seven of trauma. GOS will be assessed and recorded after 2 months.

The Glasgow outcome scale (GOS) will be used to categorize the outcome after 2 months as follows:

1- Death.
2- Persistent vegetative state: Minimal responsiveness.
3- Severe disability: Conscious but disabled; dependent on others for daily support.
4- Moderate disability: Disabled but independent; can work in sheltered setting.
5- Good recovery: Resumption of normal life despite minor deficits.

Statistical methods:

Data of 60 patients were statistically described in terms of mean, standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the MgSO4 group was done using Student *t*-test for independent samples. Comparison between the different categories of GOS at 2 months was done using Kruskal Wallis test with posthoc multiple 2-group comparisons.

For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is less than 5.

p-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Study registration:

The study was approved from ethics committee of Cairo University on April 2019 with serial number (N-142-2019).

The Study was registered prospectively in ClinicalTrails.gov under (CairoU record N- 142- 2019).

Results

This study included 60 patients with post traumatic brain injury either moderate (GCS = 9-12) or severe (GCS = 3-8) admitted in one of the neurosurgical ICU of the following centers; Kasr El-Aini Hospitals, Beni-Suef University Hospital or Beni-Suef General Hospital from April 2019 to August 2019. Patients included in the study were randomly allocated into one of two equal groups:

- Group (A): Received MgSo4.
- Group (B): Received normal saline as a placebo.

Gender distribution:

There was an evident male predominance in both groups. The difference between both groups regarding gender distribution was statistically insignificant.

Table (1): Gender distribution in each group.

	Male		Female		*p*-value
Group A	24	80%	6	20%	0.73
Group B	26	86.7%	4	13.3%	

Mortality:

There were 22 mortality cases in the whole study that represented 36.6% of the whole study group.

- In group A: 12 mortality cases.
- In group B: 10 mortality cases.

The difference was statistically insignificant

Table (2): Mortality in each group.

	Mortality	%	*p*-value
Group A	12	40	0.0787
Group B	10	33.3	

Glasgow outcome scale (GOS):

Glasgow outcome scale (GOS) after 2 months in group A was:

- Good recovery (favorable outcome): 16 cases.
- Unfavorable outcome: 14 cases as follows:
  - Moderate disability: 2 cases.
  - Death: 12 cases.

Glasgow outcome scale (GOS) after 2 months in group B was:

- Good recovery (favorable outcome): 15 cases.
- Unfavorable outcome: 15 cases as follows:
  - Moderate disability: 4 cases Severe disability: 1 case.
  - Death: 10 cases.

The difference between two groups regarding GOS was statistically insignificant.

Table (3): GOS after 2 months in both groups.

	Good recovery	Moderate disability	Severe disability	Death	*p*-value
Group A	16	2	0	12	0.598
Group B	15	4	1	10	

Table (4): Favorable versus unfavorable recovery in both groups.

	Favorable recovery	Unfavorable recovery	%	Total	*p*-value
Group A	16	14	51.6	30	0.796
Group B	15	15	48.4	30	

There was no statistically significant difference between good recovery in both groups.

- *p*-value is insignificant.

Table (5): Basic statistics in Group A.

	Mean	Standard deviation (SD)	Median	Minimum	Maximum	*p*-value
Good recovery	10.44	1.094	11.00	9	12	0.00011
Moderate disability	8.00	1.414	8.00	7	9	
Death	7.92	1.084	8.00	6	9	
Total	9.27	1.660	9	6	12	

Table (6): Correlation between admission GCS and GOS after 2 months in Group A.

GCS-Admission	GOS-2 months	Number	Mean Rank
	Death	12	8.29
	Good recovery	16	21.72
	Moderate disability	2	9.00
	Total	30	

GOS after 2 months was affected by GCS on admission; better GCS on admission was associated with better outcome after 2 months.

- *p*-value was statistically significant.

Table (7): Basic statistics in Group B.

	Mean	Standard deviation	Median	Minimum	Maximum	*p*-value
Good recovery	9.93	1.335	10.00	8	12	0.444
Moderate disability	10.00	1.826	10.00	8	12	
Severe disability	9.00	–	9.00	9	9	
Death	9.10	1.101	9.00	8	11	
Total	9.63	1.326	9.00	8	12	

Table (8): Correlation between admission GCS and GOS after 2 months in Group B.

GCS-Admission	GOS-2 months	Number	Mean Rank
	Death	10	12.5
	Good recovery	15	17.47
	Moderate disability	4	17.38
	Severe disability	1	12.000
	Total	30	

No significant relationship between GCS on admission and GOS after 2 months in this group.

- *p*-value was statistically insignificant.

In our study, Group A (received Mgso4) was associated with statistically significant correlation between GCS on admission and GOS after 2 months; with administration of Mgso4; the better GCS on admission, the better clinical outcome after 2 months.

Results of the study was released and available on clinical trials under the number NCT04646876.

Discussion

TBI is recognized as the main etiology of mortality and morbidity worldwide especially in young ages *[14]*. The annual estimate of new cases worldwide is 69 millions, most of them are of mild severity *[15,16]*.

Neuroprotection deserves to play important role in TBI due to limited options available for treatment, and the paramount effect of secondary injury in determining the final outcome *[17]*.

Martina Stippler et al., *[18]*, studied the relation between serum and CSF magnesium levels and outcome in severe TBI. They noticed that patients with low serum magnesium (<1.3mEq/L) and high CSF magnesium on admission were 2.37 times more likely to had a poorer outcome and even rapid correction did not reverse it.

In Temkin NR et al., **[19],** with a similar methodology, severe TBI patients were randomly assigned into magnesium sulphate and placebo groups. They did not use a fixed dose as in our study, rather the dose was set to reach either low or high serum magnesium levels. The therapeutic window was only 8 hours and lasted for 5 days which is different from our study where loading dose was administered within 24 hours window and continued for 48 hours. Primary outcome was assessed based on rate of mortality, seizures, functional measures, while extended Glasgow outcome scale (GOS-E) after 6 months represented the secondary outcome. Study concluded that magnesium has no neuroprotection, furthermore it might have a negative effect, in contrast to our results which showed more favorable recovery in magnesium group (non statistically significant).

Dhandapani et al., **[20]**, tested the highest daily dose (34 gm), but did not implement blinding technique. GOS after 3 months showed favorable outcome recorded in 73% of magnesium group, compared to only 40% in control group. Their results strongly supported the neuroprotective notion much more than ours, and this could be explained by dose-dependent effect.

The Blinding technique was adopted by Shakeri et al., **[21]**, who randomly allocated 38 patients in two groups. After 2 months, a statistically significant improvement of GCS and statistically insignificant improvement in motor function was recorded in the magnesium sulphate group. Their therapeutic window was only one hour after trauma and lasted for 24 hours, in contrast to our study which had a 24 hours therapeutic window with maintenance continued for 3 days. Another difference was the selection criteria which excluded all patients underwent surgical intervention in contrast to our study where patients indicated for surgical intervention were included in both study groups.

Again, a potential dose- dependent effect could explain the different results in Zhao et al., **[22]**, in their study which also excluded surgical patients, they concluded that magnesium does not significantly improve the prognosis of patients with TBI at the discharge, but may improve long-term prognosis. This is different to results of our study at which Mgso4 failed to achieve significant beneficial effect in reducing mortality in TBI patients.

A higher dose of magnesium combined with lidocaine has been also tested in Canavero et al., **[23]** with just a 12.5% mortality rate recorded compared to 36% in our study. Furthermore, Canavero et al., included only patients with severe TBI. This difference could be attributed to the potential neuroprotective mechanism of lidocaine.

Conclusion:

The study did not identify a significant beneficial effect in reducing mortality in traumatic brain injury; however, it suggested that magnesium sulfate shows a tendency to improve the outcome after 2 months as long as GCS was better on admission.

The conundrum of neuroprotection with its translation from lab to clinical world is poised to remain for longer due to multifactorial reasons encompassing different patients` criteria and research methodology. Further understanding of secondary neuronal damage pathophysiology, using objective ready measurable means like biomarkers and multi center cooperation could be of help.

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Conflicts of interest:

There are no conflicts of interest.

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سلفات الماغنيسيوم كحماية للأعصاب
فى اصابات المخ بعد الحوادث

تعتبراصابات المخ ما بعد الحوادث هى السبب الرئيسى للوفاة والاعاقات اكثر من اى اصابات جسدية اخرى وتمثل مشكلة صحية ذات تأثير كبير فى الدول المتقدمة والنامية على حد سواء.

هدف هذه الدراسة: هو تقييم دور سلفات الماغنيسيوم فى اصابات المخ مابعد الحوادث وخصوصا فى الاصابات المتوسطة والشديدة لاكتشاف قدرته على تحسين درجة الوعى وتقليل الوفيات الدراسة كانت دراسة استباقية عمياء القطبين متضمنة علاج وهمى للمقارنة وذات اختيارات عشوائية تضمنت الدراسة ٦٠ مصابا باصابات مخية سواء متوسطة (٩-١٢ عى مقياس جلاسجو) أو شديدة (٣-٨ على مقياس جلاسجو) الدراسة تم اجراؤها على الحالات التى تم حجزها فى رعاية جراحة المخ والأعصاب بمستشفى القصر العينى ومستشفى جامعة بنى سويف ومستشفى بنى سويف العام في المدة من شهر أبريل الى شهر أغسطس ٢٠١٩ تم تقسيم المصابين بشكل عشوائى الى مجموعتين (أ & ب) كل مجموعة تتضمن ٣٠ مصاباً المصابين بالمجموعة (أ) تلقوا سلفات الماغنيسيوم عن طريق الوريد والمجموعة (ب) تلقت العلاج الوهمى وهو محلول ملحى.

وكانت النتائج السريرية كالتالى: ٢٢ حالة وفاة في الدراسة بشكل عام وبنسبة ٣٦,٦٪ بواقع ١٢ حالة وفاة بالمجموعة (أ) و١٠ حالات وفاة بالمجموعة (ب) وبدون فرق مؤثر احصائيا كما لم تسجل الدراسة فرق مؤثر احصائياً بالنسبة لمقياس جلاسجو الممتد بعد ٦٠ يوم من الاصابة فى المجموعة (أ) تم تسجيل فرق مؤثر احصائياً بين درجة وعى المصاب عند الدخول ودرجة وعيه على مقياس جلاسجو الممتد بعد مرور ٦٠ يوما كالتالى: بالنسبة للمصابين الذين تلقوا سلفات الماغنيسيوم وكلما كانت درجة وعى المصاب أفضل عند الدخول للمستشفى بعد الاصابة كلما تحسنت حالته السريرية بعد ٦٠ يوماً.