

The Use of Magnesium Sulphate for Brain Protection in Traumatic Head Injury

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Abstract: Traumatic brain injury (TBI, also called intracranial injury) occurs when an outside force injures the brain. Traumatic Brain Injury can be classified based on severity (mild, moderate, or severe), mechanism (closed or penetrating head injury), or other features. Head injury usually refers to TBI, but is a broader category because it can involve damage to structures other than the brain, such as the scalp and skull. Traumatic brain injury is a major cause of death and disability worldwide, especially in young people. Causes include falls, vehicle accidents, and violence ⁽¹⁾. The current study describes the significance of supplemental magnesium for brain protection after traumatic brain injury. In this study, 40 adult patients with mild, moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within 8 h of injury and continuing for 5 days. Magnesium doses were targeted to achieve serum magnesium range of 4-0 mEq/L. The outcome was a composite of mortality, seizures, time of stay in hospital and functional.

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Key words: Traumatic brain injury, Magnesium sulphate, Outcome.

1. Introduction

Traumatic Brain Injury (TBI), a clinical problem treated frequently by medical community, is a major cause of disability, death, and economic cost to our society. In the past two decades, we have increased remarkably our understanding of the pathophysiology of TBI ⁽²⁾. One of the central concepts that emerged from clinical and laboratory research is that all neurological damage does not occur at the moment of impact, but The primary injuries trigger a sequence of secondary alterations in brain metabolism and ion homeostasis, intracranial hemodynamics, and brain water compartment. They may develop over a period of hours or days following initial traumatic assault. Satisfactory outcome of the patient often require recognition and successful treatment of these secondary derangements ⁽³⁾. These continuing effects of trauma, known as secondary injury are not irreversible, but Mediated by injury factors, which if identified and treated with anti-factors can prevent or at least attenuate the injury process and result in significant improvement in functional outcome after TBI⁽⁴⁾. Of these, Magnesium decline has been identified as playing a crucial role⁽⁵⁾, and its supplementation has been found to improve neurological outcome in animal models of TBI^{(6),(7)}. Magnesium is one of the agents used for brain protection. It has been shown that intraneuronal and cerebrospinal fluid magnesium levels were decreased after stroke and brain trauma. Magnesium attenuates a variety of secondary injury factors, including brain edema, cerebral vasospasms, glutamate excitotoxicity, calcium-mediated events, lipid peroxidation,

mitochondrial permeability transition, and apoptosis. Multiple studies came to the conclusion that magnesium offers more neuroprotection when administered preischemically as opposed to postischemically. It is remarkable that both MgSO₄ and MgCl₂ are neuroprotective preischemically, but only MgSO₄ is neuroprotective 8 hours after ischemia. ⁽⁸⁾

This study was undertaken to test the efficacy and safety of parenterally administered Magnesium sulphate (MgSO₄) in patients of traumatic brain injury.

2. Patient and Methods

After approval of the ethical and search committee, the study was done on 40 adult patients of both sexes in trauma intensive care unit (TICU) in AL-Azhar University Hospital, between April 2016, and January 2017.

Inclusion criteria:

Any adult patients with traumatic head injury admitted to the traumatic ICU.

Exclusion criteria:

1. Trauma patients with two or more bone fractures.
2. Patients with history of myasthenia gravis.
3. Impaired renal function.
4. Patient with previous neurological disorder.
5. Patient with cardiological disorder or C.O.P.D

After complete history taking, both anatomical and physiological assessment were documented, the Glasgow coma scale (GCS). The scores indicate the

severity of trauma as following: Severe head injury (3 to 8). Moderate injury, (9 to 12). or, Mild injury, (13 to 15.), then Respiratory care & ABGs analysis is done immediately on arrival to TICU (as pulse oximeter may be deceptive) and the decision to ventilate the patients, CVS care by keeping the patient normotensive & normovolemic, peptic ulcer prophylaxis using Ranitidine 50 mg IV, antibiotic prophylaxis, If patient develops seizures phenytoin were used as loading dose 20 mg /kg followed by daily dose 5-7 mg/kg (ideal body weight), and urinary catheterization done in all. Mannitol was given to patients with CT having evidence of focal mass effect or diffuse edema. Routine ICU monitoring as (ECG, pulse oximetry, ABGS), Routine laboratory investigations Including liver and kidney functions, CBC, Blood sugar and coagulation profile Serum electrolytes (Na⁺, K⁺, calcium (total and ionized), phosphate and Mg (Total and ionized).

Patients were randomly divided into two groups (By odd and even numbers).

Group I: Magnesium group (M): "20 patients"

The first dose of magnesium sulfate is 1 mEq /kg given IV within 8 hours of Injury then a five day continuous IV infusion of magnesium sulfate 0.24mEq/kg per hour and Daily magnesium levels are checked And the dose changes in order to keep the magnesium blood level at Approximately 4 mEq/L.

N.B.: mg = mEq x Atomic weight
valance. Where 1gram of Mg=8.12mEq.

Group II: Placebo group (P) "20 patients"

The patient received a placebo which looks just like magnesium sulfate but contains no active medication.

Outcome

The outcome will be a composite based on individual measures including mortality, seizures, and health-status measures.

Composite outcome measures

- Mortality within one week.
- The total time of stay in both ICU and hospital from aneuurological point of view.
- Early seizures (seizures occurring after randomization but by day 7 after injury).
- Late seizures (seizures occurring after day 7 after injury), (censored at one month).
- Glasgow coma scale (daily until discharge).
- Glasgow outcome scale-extended (at time of discharge).

Statistical analysis:

Data are presented as mean (SD) parametric and non-parametric versions of ANOVA test will be used for analysis of continuous and discrete data, as appropriate, with post tests done if significance is detected.

P value < 0.05 will consider statistically significant.

3. Results

Our results of study show in general a significant association of MgSO₄ with favorable outcome as previously seen in experimental studies. Our study was a single-center, randomized, parallel group, double-blind Trial. Randomization was stratified by severity (mild, moderate and Severe) according to Glasgow coma Scale (mild from 13-15, Moderate from 9-12 and severe from 3-8).

Table 1: Characteristics of patients enrolled, Data are represented as number (& %)

Criterion		Groups				Chi-Square	
		Magnesium group		Placebo group		T or X ²	P-value
Age	Range	18	55	18	59	-1.729	0.092
	Mean± SD	29.850	9.912	36.300	13.425		
Sex	Male	15	75.00	16	80.00	0.143	0.705
	Female	5	25.00	4	20.00		
Trauma	Blunt	15	75.00	15	75.00	0.000	1.000
	Penetrating	5	25.00	5	25.00		
Time from injury to study drug	Loaded ≤ 4 h	4	20.00	4	20.00	0.000	1.000
	Loaded >4 h	16	80.00	16	80.00		

-Baseline characteristics were quite well balanced between magnesium and placebo groups

- Most patients were young men; and most patients were randomised in the moderate injury stratum.

-Average time from injury to initial study drug bolus was 5.4 h (SD 1.5).

Our study is a controlled study on 40 patients, where we aimed to divide patients randomly into two groups:

Group I: Magnesium group (M): "20 patients"
The first dose of magnesium sulfate is given

intravenous within 8 hours of injury then a five day continuous intravenous infusion of magnesium sulfate 0.24 mEq/kg per hour. And the dose changes in order to keep the magnesium blood level at approximately 4 mEq/L.

Group II: Placebo group (P)” 20 patients “The patient received a placebo which looks just like magnesium Sulfate but contains no active medication.

Most patients in our study were young men which consistent with the epidemiology of traumatic brain injury ⁽⁹⁾, and most patients were randomized in the moderate injury stratum.

Table 2: Criteria of patients on admission to ICU Data are represented as mean (± SD)

		Groups				Chi-Square	
		Magnesium group		Placebo group		T or X ²	P-value
Systolic blood pressure before dosing	Range	90	165	90	155	0.084	0.934
	Mean± SD	123.750	19.793	123.250	18.011		
Diastolic blood pressure before dosing	Range	50	90	50	90	0.760	0.452
	Mean± SD	73.750	11.456	71.000	11.425		
Heart rate (beats/minute)	Range	55	98	68	88	0.355	0.725
	Mean± SD	76.950	13.866	75.750	6.069		
Respiratory rate before dosing	Range	11	22	10	20	1.976	0.055
	Mean± SD	17.050	3.268	15.000	3.293		
Baseline serum magnesium in m Eq/L	Below lower limit of normal	9	45.00%	10	50.00%	0.100	0.752
	At least normal	11	55.00%	10	50.00%		

- The results show no statistical significance difference.

-Average total magnesium concentrations were 3.9 mEq/L (SD 0.35) in the magnesium group and 2.25 mEq/L (SD 0.25) in the placebo group.

-For ionised magnesium, the values were 3.35 mEq/L (SD 0.5) in the magnesium group and 1.35 mEq/L (SD 0.24) in placebo groups.

Table 3: Patients according to severity determined by GCSData are represented as number (%)

Severity	Groups				Chi-Square	
	Magnesium group		Placebo group		X ²	P-value
	N	%	N	%		
Mild GCS = 13-15	4	20.00%	3	15.00%	0.143	0.705
Moderate GCS =9-12	12	60.00%	13	65.00%	0.040	0.841
Severe GCS =3-8	4	20.00%	4	20.00%	0.000	1.000
Total	20	100.00%	20	100.00%	0.183	0.913

Table 4: Patient’s mortality. Data are represented as number (%)

Severity	Groups				Chi-Square	
	Magnesium group		Placebo group		X ²	P-value
	N	%	N	%		
Mild	2	28.57%	0	0.00%	1.071	0.301
Moderate	2	28.57%	9	90.00%	4.380	0.036*
Severe	3	42.86%	1	10.00%	0.982	0.322
Total	7	100.00%	10	100.00%	7.148	0.028*

(P* = significant)

- There is significant difference between Magnesium and Placebo groups in the moderate GCS category as regards total mortality.

Table 5: Early and late seizures occurring in patients of the study. Data are represented as number (%)

Severity	Magnesium group				Placebo group				Chi-Square	
	Early seizures		Late seizures		Early seizures		Late seizures		X ²	P-value
	N	%	N	%	N	%	N	%		
Mild	0	0.00%	2	10.00%	3	15.00%	1	5.00%	3.819	0.049*
Moderate	3	15.00%	5	25.00%	12	60.00%	1	5.00%	4.851	0.028*
Severe	3	15.00%	1	5.00%	0	0.00%	4	20.00%	4.800	0.028*

(P* = significant)

- Early seizures and late seizures were significantly less in all the magnesium groups, mild, moderate and severe groups.

Table 6: Glasgow outcome scale (extended 1 month) “Data are represented in mean and SD”

severity	Magnesium group		Placebo group		T-Test	
	Mean	SD	Mean	SD	t	P-value
Mild	6.885	0.515	6.477	0.475	1.070	0.333
Moderate	5.603	0.490	4.801	1.214	2.131	0.044*
Severe	4.230	0.054	4.310	0.927	-0.172	0.869
Total	5.585	0.961	5.073	1.237	1.462	0.152

(P* = significant)

- Glasgow outcome scale-extended scores yielded significant results in the moderate group.

Table 7: Time of stay in the hospital and ICU “Excluding mortality cases “

Criterion	Magnesium group (M)				Placebo group (P)				P value
	total	mild	moderate	severe	total	mild	moderate	severe	
≤ 1 week	1(5%)	1(5%)	2(10%)	2(10%)	P=1.000
1-2 weeks	3(15%)	1(5%)	2(10%)	3(15%)	1(5%)	2(10%)	P=1.000
2-3 weeks	5(25%)	5(25%)	2(10%)	2(10%)	P=0.086
3-4 weeks	3(15%)	2(10%)	1(5%)	2(10%)	2(10%)	P=0.820
> 4 weeks	1(5%)	1(5%)	1(5%)	1(5%)	P=0.049*

(P* = significant)

-Regarding the time of stay in hospital and ICU there was significant difference between magnesium and placebo groups after 4 weeks of hospital stay (P=0.049).

4. Discussion

Traumatic brain injury (TBI) is a process beginning with an initial impact followed by Secondary events in four overlapping phases- primary injury, evolution of the primary Injury, secondary injury and recovery. ⁽¹⁰⁾

Unfortunately the clinical trials that have attempted to inhibit individual secondary factors ⁽¹¹⁾⁽¹²⁾⁽¹³⁾ lipid peroxidation, free radical injury, calcium influx, glutamate excitotoxicity, apoptosis, and edema have met with very limited success due to the heterogeneous nature of secondary injury ⁽¹⁴⁾ that includes secondary mass lesions and edema ⁽¹⁵⁾, secondary ischemic brain damage ⁽¹⁶⁾ and secondary axonal injury. ⁽¹⁷⁾

Magnesium is the second most abundant intracellular cation and is present in more than 300 enzymatic systems, crucial for ATP metabolism and protein synthesis and is also an essential transmembrane and intracellular modulator of electrical activity ⁽¹⁸⁾ It affects a number of secondary injury factors ⁽¹⁹⁾, the most predominant action is being on NMDA excitotoxicity either by receptor blockade ⁽²⁰⁾, or by decreasing glutamate release ⁽²¹⁾.

The other neuro-protective mechanisms proposed are calcium channel antagonism ⁽²²⁾, Maintenance of cerebral blood flow ⁽²³⁾, apoptosis prevention ⁽²⁴⁾, and amyloid precursor Protein upregulation ⁽²⁵⁾.

Vink *et al*, in 1987, demonstrated 70% decline of intracellular free Mg²⁺ in the cortex of brain-injured

rats, within the first hour of injury and non-recovery of the same over the Next 3 hours⁽²⁶⁾. They later demonstrated its correlation with functional outcome.⁽²⁷⁾ In a small group of patients with severe TBI, plasma total Mg was found to be low.⁽²⁸⁾ Parallel decrease in free ionized Mg²⁺ has been found in animal⁽²⁹⁾ and human⁽³⁰⁾ studies which correlated with the outcome⁽²⁹⁾ and severity⁽³⁰⁾. This is most likely due to enhanced glucose metabolism by glycolysis⁽³¹⁾⁽³²⁾ and can also be due to urinary losses.⁽²⁸⁾ Supporting experimental studies have also demonstrated that inducing a brain Mg deficiency prior to injury exacerbates the functional deficits and that attenuating the post-traumatic decline attenuates the functional deficits after TBI⁽³³⁾.

Administration of Mg salts after experimental TBI was found to improve neurological Outcome, both with respect to motor and cognitive performance⁸. It was also noted that Mg treatment reduced the volume of cortical histological lesion following Experimental TBI in rats.⁽³⁴⁾

Mortality

In our study, mortality was the main serious adverse event, at the magnesium group, the total mortality rate for the magnesium cases was significantly less than that for placebo (p value = 0.028) and also in the moderate GCS cases (p value = 0.036). However there were no significant differences in both mild (p value = 0.301) and severe cases (p value = 0.322).

Dhandapani *et al*, in 2004, in a randomized controlled study on 60 patients, 30 patients received magnesium and 30 patients were control group did not receive magnesium, they found that parenteral Magnesium sulfate appears to reduce mortality, intra-operative brain swelling, improvement in the CT lesion in the magnesium group than the control group and has favorable influence on outcome on Glasgow outcome scale at 3 months, when administered to patients presenting within 12 hours of closed traumatic brain injury with GCS 5 to 8 without any apparent significant adverse effects.⁽³⁵⁾

Canavero *et al*, in 2003, in a non-controlled study on 32 patients of severe head injury who received parenteral MgSO₄, noticed lower mortality at 6 months (12.5%)⁽³⁶⁾ As compared to other published literature (45-55%).⁽³⁷⁾

Seizures

Early seizures and late seizures were generally less in all the magnesium groups (p value = 0.040), mild (p value = 0.049), moderate (p value = 0.028) and severe (p value = 0.028).

Temkin and Anderson *et al*, In a double-blind trial, 499 patients aged 14 years or older admitted to a

regional trauma center between 1998, and 2004, with moderate or severe traumatic brain injury were randomly assigned one of two doses of magnesium or placebo within 8 h of injury and continuing for 5 days. Magnesium doses were targeted to achieve serum magnesium ranges of 1.0–1.85 mmol/L or 1.25–2.5 mmol/L. They found that Magnesium showed no significant positive effect on the composite primary outcome measure at the higher dose (mortality, seizures, functional measures and neuro-psychiatric tests at 6 months).

Those randomly assigned magnesium at the lower dose did significantly worse than those assigned placebo. Furthermore, there was higher mortality with the higher magnesium dose than with placebo. Other major medical complications were similar between groups, except for a slight excess of pulmonary edema and respiratory failure in the lower magnesium target group. No subgroups were identified in which magnesium had a significantly positive effect.

Moreover, they did not note any significantly positive treatment effects in any of the subgroup analyses. Almost all patients were given phenytoin for the first week, which would have lessened any possibility of seeing an effect of magnesium on early seizures. No laboratory work has looked at an interaction between magnesium and phenytoin, but a huge interaction would be needed to bring a study from significant in one direction to significant in the other.⁽⁹⁾

Functional outcome & Time of stay in ICU and the hospital

In our study, Glasgow outcome scale-extended scores yielded significant results in the moderate group (p value = 0.044), and no significance in mild case (p value = 0.33) or severe cases (p value = 0.869).

In our study, Regarding the time of stay in hospital and ICU there was significant difference between magnesium and placebo groups after 4 weeks of hospital stay (P=0.049).

Heath *et al*, in 1999, demonstrated a potential therapeutic window of 24 hours after trauma in rats. In their experiments, Mg therapy significantly improved motor outcome when administered up to 24 hours after injury with earlier administration resulting in more pronounced improvement. Repeated administration beyond 24 hours did not further improve outcome.⁽³⁸⁾

According to Dhandapani *et al* study, in 2004, favorable outcome of good recovery or moderate disability on Glasgow outcome scale at 3 months was observed in 22 out of 30 patients (73.3%) who had received MgSO₄, as compared with 12 out of 30 (40%) in control group. The Good recovery was seen in 14 out of 30 (46.7%) in MgSO₄ group as compared with 6 out of 30 (20%) in control group.⁽³⁵⁾ They also

found that areas of infarction were 3.4 times less frequent in the MgSO₄ group. Though statistically not significant, probably due to the small number of patients in their trial, it may be clinically relevant considering the importance of ischemia in secondary injury and the proven efficacy of MgSO₄ in delayed cerebral ischemia of SAH⁽³⁵⁾.

Among patients of Dhandapani *et al.*, in 2004, CT scan results showed favorable outcome in MgSO₄ group which was 2 times the control. Though not significant, this may reflect the possible role of Mg in attenuation of secondary axotomy.⁽³⁵⁾

McKee and colleagues, in 2005, described the function of the blood-brain barrier in patients with traumatic brain injury by using magnesium sulfate infusions initiated an average of 5 days after injury (range 1–16 days). They showed that increasing serum magnesium concentrations yielded only a marginal increase in CSF concentrations (total and ionized); they concluded that the regulation of the blood-brain barrier for magnesium remains largely intact after brain injuries.⁽³⁹⁾

Conceivably, supplementation of magnesium as part of standard care might be sufficient to obtain some beneficial effect of magnesium.⁽⁹⁾

Disruption of the blood-brain barrier is commonly observed shortly after experimental and clinical traumatic brain injury.⁽⁴⁰⁾ In rat models of traumatic brain injury, intravenous administration of magnesium 30 min post injury has been shown to result in significant increases in intracellular free magnesium brain concentrations compared with in non-treated controls.⁽⁴¹⁾ Increases in brain concentrations were linearly correlated with magnesium dose and neurological outcome as determined by the rotorod test.⁽⁴²⁾⁽⁴³⁾

Consistent with the findings in the laboratory findings in our study and in Temkin and Anderson *et al.* study, in 2004, about half of participants had a magnesium concentration below the lower limit of normal before study drug loading. About half or more of cases in the placebo group had magnesium concentration below the normal range.⁽⁹⁾

Conclusion

Parenteral magnesium sulphate by intravenous infusion within the first 8 hours after bolus dose in head trauma for the first 5 days trying to keep serum level of magnesium around 4 mEq/L appears to improve survival, reduce early and late seizures, shorten period of hospital stay in all patients with traumatic head injury, and is associated with better favorable outcome and less disability at 1 months in patients with GCS 9-12(moderate cases), without any apparent significant adverse effects.

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