DOI: https://doi.org/10.53350/pjmhs221621013

ORIGINAL ARTICLE

Importance of Magnesium Sulphate in Improvement of GCS Score after Severe Traumatic Brain Injury

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ABSTRACT

Background: Grounded on a series of studies, magnesium Sulphate (MgSO4) administered after extensive axonal damage has emerged as a valuable neuroprotective mediator. This study was held to investigate whether magnesium Sulphate had therapeutic safety and efficacy in patients with severe diffuse axonal injury and its effect on improving GCS scoring.

Methods: This double-blind, randomized and placebo-controlled clinical trial study was held from October 2020 to September 2021, patients with severe extensive damage to the axons were studied who presented to the Neurosurgery emergency of tertiary care hospital, and written knowledgeable permission was taken from all subjects. 42 patients who met the eligibility criteria were randomly assigned to our study. Adult patients with severe diffuse axonal injury within the first hour of closed traumatic brain injury (TBI) and meeting eligibility conditions were divided randomly into 2 groups. The treatment regimens contained preliminary intravenous 50 mg / kg magnesium sulfate as loading dose within one hour of injury, followed by QID 50 mg / kg magnesium sulfate up to 24 hours post-injury. The results were mortality, GCS, and assessment of motor function up to two-months after injury.

Results: Magnesium had a substantial optimistic impact on GCS after two-months (P = 0.04). The result of motor function improved more in the MgSO4 group than in the control group, but it was not statistically important (p = 0.52). Finally, it is concluded that direction of magnesium sulfate after severe DAI can play a neuroprotective role.

Keywords: Magnesium sulfate; Severe diffuse axonal injury and results.

INTRODUCTION

Traumatic Brain Injury (TBI) is the foremost reason of mortality in individuals below 45 years of age. Despite this, there is no accepted pharmacological intervention for the treatment of neurotrauma[1-2]. DAI is seen in majority of TBI individuals who are affected severely despite the absence of major parenchymal lacerations, hematomas or contusions[3]. It is characterized by many small changes in the white grey matter. Patients with DAI often find themselves in a deep coma as a consequence of trauma, do not show raised intracranial pressure, and frequently have an unfortunate prognosis[4]. The pathophysiology of diffuse axon damage involves significant acceleration and angular and rotational deceleration, resulting in shear and traction forces on the axons[5]. The histological findings of DAI are well defined and comprise edema and disruption of the axons, "retraction balls" (inflamed proximal ends of the injured axons), and punctual haemorrhage in the midbrain, corpus callosum and pons. Several of these anomalies, including severing of axons, do not occur primarily but progress within days or even hours of injury. In most patients, it is tough to differentiate damage of axons because of mechanical shear (primary damage) and secondary damage due to the metabolic and biochemical consequences of TBI. Based on the results of in vivo studies, neuroprotective therapy will play a key role in the pathophysiology of DAI[6-7]. Empirically, analysis from numerous laboratories have recognised reductions in brain and serum magnesium levels following traumatic brain injury in experiments, and that this reduction in intracellular Mg is associated with decreased cellular phosphate energy stores and severity of the injury[8-9]. Magnesium supplementation improves results, whether it is administered shortly after, before or several hours afterwards the injury. Mg is believed to act presynaptically to inhibit excitatory amino acid release (EAAS) and postsynaptically through non-competitive, voltage-dependent inhibition of Ca release via the N-methyl-D-aspartate (NMDA) receptor, a mechanism attributed to neural effects[10]. Therefore, brain injuries related to EAA excitotoxicity, such as global ischemia and traumatic brain injury, provide an opportunity to assess this potential neuroprotective mechanism with Mg[11]. Inappropriately, many trainings assessing the magnesium effects are restricted to the 1-2 weeks post-injury period, so it is indistinct that the observed functional improvement is related to long-term outcome functionally or merely to the momentary nature of the disease[12]. Therefore, we designed this study to trial the concept that treating diffuse axon damage with magnesium in head injury patients will improve short- and long-term outcomes following the injury and its effect on improving GCS scoring.

MATERIALS AND METHODS

This double-blind, randomized and placebo-controlled clinical trial study was held from October 2020 to September 2021, patients with severe extensive damage to the axons were studied who presented to the Neurosurgery emergency of tertiary care hospital, and written knowledgeable permission was taken from all subjects. This ethical committee approved the study. The inclusion criteria were: patients over 20-68 years of age, the time between the injury and admission to a medical center preferably no longer than an hour. Severe diffuse injury of axons was distinct as a coma remains for more than 24 hours with flaccidity and posturing. None of our patients regained consciousness within the first 24 hours in routine monitoring in the intensive care unit. In fact, they were excluded if they recovered. Exclusion criteria were renal failure, pregnancy, convulsions, unstable cardiovascular status, surgical indications for evacuation of intracranial hematoma, persistent hypotension unresponsive to intravenous fluid administration (systolic blood pressure <90 mmHg), refractory systemic bleeding requiring blood transfusion, traumatic subdural hematoma and surgical removal of intraperitoneal bleeding. All patients were treated with ventilation, antibiotic prophylaxis with cefotaxime or ceftriaxone, prophylaxis of seizures with phenytoin, prophylaxis of gastric ulcers with ranitidine, and urinary catheterization. Randomisation was stratified by severity and age. 42 patients who met the eligibility criteria were randomly assigned to our study. The treatment regimens contained preliminary intravenous 50 mg / kg magnesium sulfate as loading dose within one hour of injury, followed by QID 50 mg / kg magnesium sulfate up to 24 hours post-injury. The control group was administered saline in the same manner. While performing routine ICU monitoring in all patients, safety can be assessed through continuous monitoring of vital signs, blood chemistry, biochemical markers, electrocardiogram, invasive blood pressure (mean, systolic, and diastolic), and continuous surveillance, clockwise improvement / output measurements. No patient has serum creatinine up to 1 mg / dL during this study. Therefore, measurement of serum magnesium was not in details. More specifically, parenteral magnesium is almost completely eliminated by renal excretion, and magnesium poisoning is unusual when the glomerular filtration rate is

maintained or only slightly reduced. Adequate diuresis is usually associated with a preserved glomerular filtration rate. This means that excretion of magnesium is not dependent on urine flow, and the volume of urine per unit time is not predictive of kidney function. therefore, serum creatinine should be measured to detect signs of decreased glomerular filtration. Outcome was assessed by certain indicators including mortality, GCS, and motor scores on days 1, 3, 10 (or on discharge after admission). Two months after injury, participants were followed in OPD for the same measures including mortality, motor function, and GCS scores. Our analysis was held in agreement with the standards of treatment. Patients not fit for follow-up were excluded from the analysis. Therefore, the sample of 42 patients was randomly divided into two groups. Data were then collected at baseline, day three, and at discharge. SPSSTM-21 was used as the statistical program. The chi-square test was applied for qualitative and quantitative variables. We used a repeated measures model (nested model) to perform the analysis with the Minitab statistical package. Our model is "GCS Change = Patients + Duration + Drug (Time) + Error". The significance level was found to be 0.05. Final results are accessible as Mean ± SE (mean standard error).

RESULTS

42 patients who were admitted during the study and met our criteria were divided randomly into 2 groups. The patients mean age in the study and control groups was 35.01 ± 2.98 and 34.80 ± 2.35, correspondingly, and no substantial age difference between the two groups (p = 0.57).

Table 1: Mean GCS variations in drug and placebo group at different times (Data are presented as Mean ± SD.)

Placebo	$MgSO_4$	Time
5.102 ± 0.25	5.345 ± 0.22	Beginning
6.654 ± 0.81	7.651 ± 0.88	3 days
8.345 ±1.12	9.731 ± 1.17	Discharge
9.654 ±1.23	11.912 ± 1.28	60 days

Our outcomes exhibited that the mean GCS recordings performed 3 times in both groups showed an increasing pattern, but not important change (P> 0.05) in the MgSO4 group, but became statistically significant (P = 0.040) (Table 1) when followed for 2 months. The results of motor function improved more than the results in the control group in the MgSO4 group, but it was not important change was noticed (p = 0.52) (Table 2). The effect of MgSO4 on the improvement of mortality was not statistically significant in any of the groups (P = 0.5).

Table 2: Mean motor variations in drug and placebo groups at different times (Data are presented as Mean ± SD.)

Placebo	$MgSO_4$	Time
3.796 ± 0.25	3.124 ± 0.16	Beginning
3.159 ± 0.434	3.368 ± 0.39	3 days
4.298 ± 0.54	4.498 ± 0.52	Discharge
4.581 ± 0.55	5.375 ± 0.52	60 days

DISCUSSION

The original concept of neuroprotection was to initiate treatment before the event occurred, and aimed to minimize the intensity or immediate effects of brain injury by disrupting the devastating cascade of biochemical events[13]. Human observations suggest that abnormal Mg homeostasis occurs under conditions of critical illness, particularly acute brain injury. Correlations between the severity of neurological deficits and the early measurement of serum Mg after traumatic brain injury were observed[14]. Hypomagnesaemia has been shown to be more common in patients with head trauma than in controls without brain damage. In patients with TBI, the severity of the injury was linearly correlated with the level of systemic ionized Mg deficiency[15]. The classic concept that DAI is caused by mechanical abduction of axons that are mismatched with repair or regeneration has now been abandoned[16]. Neurons can at minimum regenerate partially their anatomy of axons. This is in line with clinical explanations that the condition of patients with DAI CT imaging features can be improved with up-to-date care of neuroendocrine[17-18]. In addition, laboratory trainings have revealed that DAI takes up to 48 hours to completely developed and is therefore acquiescent to therapeutic intervention. In this study, it was shown that a repeated application after 24 hours did not improve the results. We applied an intravenous maintenance regimen up to 24 hours after the injury[19-20]. Earlier results have shown that administration of magnesium sulfate in low or high doses cannot improve neurological outcomes, at least when administered in low doses. We find worse outcome with higher dose and higher mortality. On the other hand, the data showed that NMDA glutamate receptor over activity occurred within the initial 1st hour later to experimental brain injury, but NMDA receptors stimulation within 24 hours and 48 hours after injury improved the results[21]. Sustained high levels of magnesium during this sub-acute period will weaken this stimulation of NMDA and possibly harmfully impact on recovery. Therefore, our interference comprised of preliminary intravenous magnesium as a loading dose followed by an intermittent infusion to maintain the magnesium concentration[22]. In this study, we verified only some of the probable dose combinations, duration and onset of treatment. Though, the design used in this study was within the range used in positive preclinical studies. MgSO4 started within 1 hour and showed a positive effect on motor function score[23]. The aim of our study was to obtain a safe treatment regimen with a positive result. Although our results showed that MgSO4 significantly improved the GCS score after 2 months, we did not reach this conclusion in terms of motor performance scores or the mortality rate. It should be noted that the GCS score may fluctuate soon after the injury, with worsening in some patients and improvement in others. From a forecasting perspective, the GCS assessment should refer to a given period based on the forecasting objective[24-25].

CONCLUSION

As the processes of cell damage are already known in the DAI and the laboratory results confirm the 48-hour period of axonal stabilization, parenteral administration of magnesium sulfate appears to have a positive effect on the GCS result after 2 months. Patients within 24 hours of closed traumatic brain injury with no apparent side effects.

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