

Magnesium Sulfate Effect on the Clinical Course and GCS of Patients with a Severe Diffuse Axonal Injury

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ABSTRACT

Based on a number of studies, magnesium sulfate (MgSO₄) given after a diffuse axonal injury has gained attention as a useful neuroprotective agent. The present study was conducted to examine if magnesium sulfate has a therapeutic efficacy and safety in patients with a severe diffuse axonal injury. Adult patients admitted within 1 hour of a closed Traumatic Brain Injury (TBI) with a severe diffuse axonal injury that met eligibility criteria were randomized into two groups. Our treatment guidelines consisted of an initial loading dose of 50 mg/kg magnesium sulfate and then 50 mg/kg QID up to 24 hours after the trauma. The outcome measures were mortality, GCS, and motor function scores which were assessed up to 2 months after the trauma. Magnesium showed a significant positive effect on GCS 2 months (P=0.03). Among those in MgSO₄ group, motor functioning score improved more than control group but this was not statistically significant (P = 0.51). At the end, we have demonstrated that administration of magnesium sulfate can have neuroprotective role following severe DAI.

Keywords: Severe diffuse axonal injury; Magnesium sulfate; Outcome

INTRODUCTION

Traumatic brain injury (TBI) is the biggest killer of individuals under 44 years of age. Despite this, there is no accepted pharmacological intervention for the treatment of neurotrauma [1; 2]. DAI is responsible for most TBI patients that are severely impaired despite the lack of gross parenchymal contusions, lacerations, or hematomas [3]. It is characterized by multiple small lesions in white matter tracts. Patients with DAI are usually in a profound coma as a result of injury, do not manifest high ICP, and often have a poor outcome [4]. The pathophysiology of diffuse axonal injury involves a severe angular and rotational acceleration and deceleration that deliver shear and tensile forces to axons [5]. The histological findings of DAI have been well described and include disruption and swelling of axons, "retraction balls" (swollen proximal ends of severed axons), and punctate hemorrhage in pons, midbrain, and corpus callosum [6]. Many of these abnormalities, including axonal severing, are not present initially but develop over a course of several hours or days after

injury [7]. In many cases, it is difficult to distinguish an axonal damage due to the mechanical shearing (primary injury) from the damage caused by biochemical and metabolic sequelae of TBI (secondary injury) [8]. According to in vivo findings, a neuroprotective therapy would play a central part in pathophysiology of DAI [9]. Experimentally, studies from several laboratories have documented that serum magnesium and brain magnesium are decreased after an experimental traumatic brain injury and this decline of intracellular Mg is associated with decreased cellular phosphate energy stores and the severity of neuronal injury [10]. Magnesium supplementation improves the outcome whether given before, shortly after, or hours after an injury. Mg is believed to act presynaptically to inhibit the release of excitatory amino acid (EAA) and postsynaptically through non-competitive voltage-dependent inhibition of N-methyl-D-aspartate (NMDA) receptor-mediated Ca release, which is the mechanism attributed to neuronal effects [11]. Therefore, brain injuries associated with EAA

excitotoxicity, such as global ischemia and traumatic brain injury, offer opportunities to evaluate this mechanism of potential neuroprotection by Mg [12]. Unfortunately most studies examining the effects of magnesium have been limited to the immediate 1-2 week period after trauma, making it unclear whether the functional improvement observed is relevant to a long-term functional outcome or simply related to the transient nature of a secondary injury [13]. So, we designed this study to test the notion that treating a diffuse axonal injury in head-injured patients with magnesium would improve outcome in short and long term after trauma.

MATERIALS AND METHODS

Patients with a severe diffuse axonal injury who were admitted to Imam Reza hospital, Tabriz, from July 2010 to July 2011 were studied. Written consent was obtained from all the patients. This study was approved by ethic committee of Tabriz University of medical sciences. Inclusion criteria were: patients older than 18 and less than 65 years old, the time gap between trauma and admission to the medical center not exceeding more than one hour preferably. Severe diffuse axonal injury was defined as a coma lasting more than 24 hours with decerebrate posturing or flaccidity. With routine ICU monitoring none of our patients recovered in consciousness during the first 24 hours. In fact they were excluded if they recovered. Our exclusion criteria were renal failure, pregnancy, seizure, unstable cardiovascular state, surgical indication for intracranial hematoma evacuation, persistent hypotension (systolic Bp < 90 mmHg) unresponsive to IV administration of fluids, refractory systemic hemorrhage requiring blood product transfusion, the presence of a traumatic subdural hematoma and operative evacuation of intracranial hemorrhage. The initial treatment consisted of ventilation, antibiotic prophylaxis with cefotaxime or ceftriaxone, seizure prophylaxis with phenytoin, gastric ulcer prophylaxis with ranitidine and urinary catheterization done in all patients. The study was a double blind randomized clinical trial with a placebo control. Randomization was stratified by severity and age. Thirty eight patients who met the eligibility criteria were

randomly assigned to our study. Our treatment guidelines consisted of an initial intravenous loading dose of 50 mg/kg magnesium sulfate within one hour after trauma and then 50 mg/kg QID magnesium sulfate up to 24 hours after trauma. Identical appearing saline was given to the control group in the same manner. With routine ICU monitoring which was performed in all the patient, the safety could be evaluated by the continuous monitoring of vital functions, blood chemistry, biochemical indices, electrocardiogram, invasive arterial blood pressure (mean, systolic and diastolic), and round-the-clock input/output measurements. During this study, we had no serum creatinine up to 1mg/dl. So, there was no need to measure the serum magnesium in more detail. Parentally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is unusual when the glomerular filtration rate is maintained or only slightly decreased. Adequate urine output is usually correlated with preserved glomerular filtration rate. That means, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not predict renal function. thus, serum creatinine levels must be measured to detect signs of declining glomerular filtration rate [21]. The outcome was evaluated on the basis of some measures including mortality, GCS, and motor function scores obtained on the first, third, tenth days (or at the discharge time after admission). Two months after the injury, the participants were followed by a phone call for the same measures including mortality, motor function and GCS scores. Our analysis followed according to the treatment principles. Patients who were not available for the follow-up were excluded from the analysis. So a sample size of thirty eight patients was selected randomly in two groups. Then the data were collected for three times: at the beginning of the study, on the third day, and at the discharge time. SPSS 17 was used as the statistical program. Chi-square test was used for qualitative and quantitative variables. We used a repeated measuring model (nested model) that would do the analysis with a Minitab Statistical Package. Our model was "Variation of GCS = patients + time + drug (time) + error". The level of significance emerged to be 0.05. Finally, the results were

presented with Mean \pm SE (standard error of mean).

RESULTS

Fifty four patients admitted during the study timeline and meeting our criteria were randomized in two groups. In the test group, two patients did not receive MgSO₄ due to renal failure, four due to refractory systemic hemorrhage requiring blood product transfusion, and six others were missing for the follow-up. In the control group, four patients were not available to follow up. The final study sample size consisted of thirty eight patients, with nineteen in each group. Mean age of patients in case and control groups was 34.72 ± 3.37 and 35.42 ± 2.48 respectively that showed no significant difference in terms of age between the two groups ($P = 0.567$). Our results showed that the mean of GCS recordings conducted at 3 times in the two groups had an ascending pattern, but it was not statistically significant in the MgSO₄ group ($P > 0.05$) But when they were followed up for 2 months it became statistically significant ($P = 0.038$) (Table 1) (Figure 1). Among those in the MgSO₄ group, the motor function scores improved more than the scores in the control group, but this was not statistically significant ($P = 0.512$) (Table 2). The effect of MgSO₄ on the improvement of mortality rate was not statistically significant in both groups ($P = 0.5$).

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

Placebo	MgSO ₄	Time
5.211 \pm 0.249	5.105 \pm 0.215	Beginning
6.947 \pm 0.807	7.632 \pm 0.873	3 days
8.526 \pm 1.173	10.895 \pm 1.169	Discharge
9.580 \pm 1.226	12.474 \pm 1.276	60 days

Table2. Mean motor variations in drug and placebo groups at different times(Data are presented as Mean \pm SD.)

Placebo	MgSO ₄	Time
3.211 \pm 0.249	3.000 \pm 0.153	Beginning
3.842 \pm 0.434	3.947 \pm 0.386	3 days
4.263 \pm 0.534	4.947 \pm 0.510	Discharge
4.421 \pm 0.548	5.053 \pm 0.516	60 days

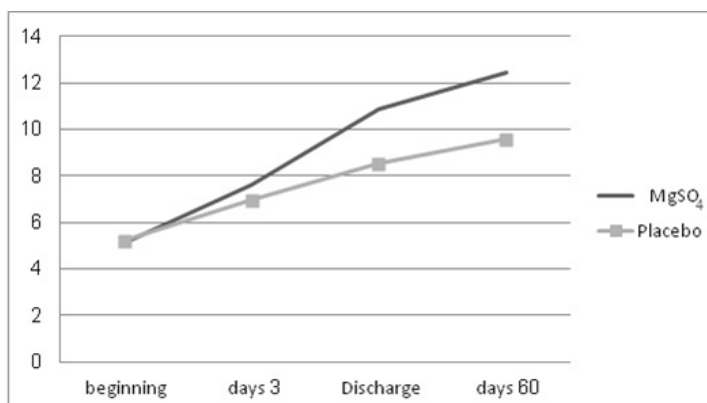


Figure 1. Mean GCS variations in drug and placebo group at different times

DISCUSSION

The original concept of neuroprotection involved the initiation of treatment before the onset of the event, and was aimed at minimizing the intensity of an insult or its immediate effects on the brain by interrupting the harmful cascades of biochemical events [14]. Observation in humans suggests that abnormal Mg homeostasis occurs in the setting of a critical illness particularly an acute brain injury. Correlations between the severity of neurological deficits and early measure of serum Mg have been observed following traumatic brain injuries [15]. Hypomagnesemia was shown to be more prevalent in patients with a head injury than in control group members without a brain injury. The injury severity in patients with a traumatic brain injury correlated linearly with the level of systemic ionized Mg depletion [16]. The classical concept that DAI is due to the mechanical rupture of axons incompatible with regeneration or repair has now been abandoned. Neurons can at least partially regenerate their axonal anatomy. This conforms to clinical observations that patients with hallmark features on CT of DAI can recover with modern neurocritical care. Furthermore, laboratory studies have shown that DAI can take up to 48 hours to become fully established and is, thus, amenable to therapeutic intervention [17]. Heath et al. demonstrated a potential therapeutic window of 24 hours after trauma in rats. In their experiments, Mg therapy significantly improved the motor outcome when administered up to 24 hours after the injury, with an earlier administration resulting in better pronounced improvement [18]. In this study, it was demonstrated that repeated administration

beyond 24 hours does not further improve the outcome. We have used a maintenance intravenous regimen up to 24 hours after injury. Previous results have shown that administration of magnesium sulfate at either a low or a high dose cannot improve neurologic outcome, at least when given at a low dose. We encounter a poorer outcome at a high dose, and a higher mortality occurs [19]. On the other hand, the data have shown that the hyperactivity of the glutamate NMDA receptor occurs within the first hour after an experimental brain injury, but the stimulation of NMDA receptors within 24 h and 48 h after the injury improves the outcome. Continuous high concentrations of magnesium in this subacute period would attenuate this NMDA stimulation and plausibly adversely affect recovery [20]. Therefore, our intervention consisted of an initial intravenous loading dose of magnesium which was followed by a non-continuous infusion to maintain the magnesium concentration. In this study we tested only a few of the possible combinations of dose, start time, and duration of treatment. However, the regimen used in this study was within the range used in positive preclinical studies. MgSO₄ started within 1h and showed a positive effect on the motor function score. The objective of our study was to achieve a safe regimen with a

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favorable outcome. Although our results demonstrated that MgSO₄ significantly improves GCS score within 2 months, we have not achieved this result about motor function scores or mortality rate. It should be noted that GCS scores may fluctuate soon after injury, with some patients deteriorating and others improving. From a perspective of prognosis, the assessment of GCS should, therefore, be related to the given time period, depending on the intent for the estimating of prognosis.

CONCLUSION

Since cell-deteriorating processes are already known in DAI, and laboratory findings confirm the 48-hour period of axonal stabilization, it is suggested that the parenteral administration of magnesium sulfate appear to have a favorable influence on GCS score at 2 months, when administered to patients within 24 hour of closed traumatic brain injury without any apparent significant adverse effects.

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