Effect Of Magnesium –Lidocaine Combination On Outcome After Severe Head Injury

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ABSTRACT

Background: *neuroprotection in the setting of severe head injury (SHI) remains unsettled problem. Our aim was to evaluate the efficacy and safety of a high dose magnesium and low dose lidocaine infused, over 3 days after SHI*

Methods: *Sixty adult patients with SHI (Glasgow Coma Scale ≤ 8) admitted to Intensive Care Unit were included in this study. Patients were divided into two groups (30 patients in each), magnesium–lidocaine (Mg-Lid) group received magnesium sulfate (70 mg/kg IV bolus followed by 15 mg/kg/hr) plus lidocaine (1.5 mg /kg bolus IV followed by 1 mg /kg/hr) infused for 3 days and control group received placebo.*

Routine monitoring and laboratory investigations were obtained immediately after admission and every 24 hours thereafter for 3 consecutive days. These include vital signs, CT scan, GCS, serum glucose, serum electrolytes, creatinine, HCO3, and bilirubin. The outcome was estimated at 6 months using the Glasgow Outcome Scale (GOS).

Results: *The serum concentrations of ionized magnesium in the Mg-Lid group were significantly increased in all subsequent values as compared with baseline value and control group. The other assessed parameters were not changed from admission.*

Patients in the Mg-Lid group had a more favorable outcome (54%) when compared to the control group (38%).Mortality rate was significantly lower in the Mg- Lid group (27%) compared with the control group (46%).

In conclusion, *magnesium-lidocaine combination administered according to the above regimen is safe and well tolerated after SHI. Patients in the Mg-Lid group showed a more favorable outcome and lower mortality rate when compared to the control group*

Key words: *Magnesium, lidocaine, severe head injury, neuroprotection*

INTRODUCTION

Traumatic brain injury is the major cause of death and disability in all age groups. Severe head injury (SHI- defined as a Glasgow Coma Scale ≤ 8 on admission) carries a 44% mortality rate according to the Trauma Coma Data Bank[1]. Prompt treatment in the first hours post- SHI may alter the final outcome[2,3]. In the past 10 years, a number of pharmacotherapies have undergone clinical trial in traumatic brain injury (TBI), particularly antiglutamatergic drugs such as magnesium. Magnesium is involved in multiple physiological processes that may be relevant to cerebral ischemia, including antagonism of glutamate release, N-methyl D-aspartate (NMDA) receptors blockade, calcium channel antagonism, & maintenance of cerebral blood flow[3].

It appears that protection of central nervous system (CNS) white matter tracts is essential for maximizing clinical recovery: axons do not contain receptor complexes or synapses so that NMDA blockade would be ineffective. Moreover, in animals, anti-NMDA drugs limit damage only in models of focal-not global –cerebral ischemia. Central myelinated axons are damaged by anoxia-ischemia in a calcium dependent manner. Leakage of Na^+ into the axoplasm through Na^+ channels cause calcium overload mainly by reverse Na^+-Ca^{++} exchange. Na^+ channel blockers are neuroprotective in animal models of brain injury[1, 4, 5].

If neuronal loss can partly be compensated by local sprouting or other mechanisms, there is no way to regenerate lost axons. Na^+ influx is the first step in the ischemic cascade[2,4], and ischemia is among the most important factors worsening TBI[2,3,4]. At the same time, it is known that CNS glutamate levels increase after TBI, leading to neuronal death[2,3,4]. Thus, it is surmised that maximal neuroprotection combines an antiglutamate

agent (e.g., Mg^{++}) plus a Na^{+} channel blocker (lidocaine). Magnesium is inexpensive, easily available, and has no adverse effects seen with anti-NMDA agents employed in clinical trials (e.g., psychotic)[6,7].

AIM OF THE WORK

The aim of this study was to evaluate the safety and the efficacy of Magnesium Sulfate (MgSO4) and lidocaine on the outcome of patients with severe head injury when infused continuously for 3 days.

PATIENTS AND METHODS

This study was carried out in the surgical ICU at Minia University Hospital after obtaining approval from the local ethics committee and written informed consent from relatives of the patients. This study was done in the period between November 2004 to march 2006.

Inclusion criteria

Patients were eligible for the study if they met the following criteria:

1- Severe head injury (SHI) with or without associated body lesions a result of car accident or accidental falls
2- Glasgow Coma Scale (GCS) score 3-8 and or CT evidence of edema.
3- Rapid deterioration if GCS drop by two point from base admission
4- Age older than 12 years old.

Exclusion criteria included

1- Renal insufficiency (creatinine>2 mg /dl).
2- Pregnancy.
3- Medical contraindication to the study drugs.

Participants

Sixty patients of both sexes were randomized to either the magnesium-lidocaine group (n=30) or the control group (n=30).

Magnesium-Lidocaine group:

Patients in this group received magnesium sulfate and lidocaine by continuous iv infusion. The magnesium-lidocaine infusion was based on the method previously proposed by Canavero et al.[8], a 3-day infusion of MgSO4 (70 mg/kg iv bolus followed by 15 mg/kg/hr) plus lidocaine (1.5 mg/kg iv bolus followed by 1 mg/kg/hr).

Control group:

Patients were given a comparable amount of normal saline and did not receive any Mg-lid supplements.

Initially, patients received care and management of SHI according to standard guidelines[3]. Hematomas were evacuated as needed. On admission 18 patients in the magnesium-lidocaine group were scored 3-5 and 8 patients GCS 6-8 compared to 16 patients in the control group were scored 3-5 and 10 patients GCS 6-8.

At admission, CT scan demonstrated that all patients had different degrees of brain edema, 11 & 9 patients had Subarachnoid hemorrhage, 4 & 5 patients had subdural hematoma, and 6 & 8 patients had brain contusion in Mg-lid group and control group respectively.

Assessment

Baseline characteristics, including age, gender, and duration of stay in ICU was recorded. Routine ICU monitoring including hemodynamic parameters, ECG, 24 hour fluid input/ output measurements, blood chemistries including blood glucose, serum sodium, potassium, creatinine, arterial HCO3, and serum bilirubin were obtained. An automated Potentiometeric Analyzer, NOVA 8 Electrolyte Analyzer (NOVA Biochemical's, Mississauga, Canada) was used to measure serum ionized magnesium. Safety was evaluated by continuous monitoring of vital functions, blood chemistry, organ function indices and electrolyte balance .

Jennett & Bond[9], presented the Glasgow outcome scale (GOS) which is a measure of disability following severe head injury that takes in account both physical and mental impairment. The five-point scale (GOS) including: (1) death, (2) permanent vegetative state, (3) severe disability (conscious but disable), (4) moderate disability (disabled but independent), and (5) good recovery, and they were recorded at 6 months.

Statistical analysis

All data were tabulated. SPSS (software package for statistical analysis) version 11 was used. Categorical data were expressed

as number and percent. Numerical data were expressed as mean and standard deviation (SD). Chi square test was used to calculate p-value of comparisons between categorical data (e.g. sex, mortality). Unpaired t-test was used to compare independent two groups of numerical data. Mann-Whitney test was used to compare nonparametric data (e.g. GCS). P-value was considered to be significant if $p < 0.05$.

RESULTS

A total of 60 patients were randomized to either the magnesium-lidocaine group or the control group. Four patients in the magnesium-lidocaine group were excluded from the analysis, three patients because of early death and one patient because of incomplete data collection on day one. Four patients were also excluded in the control group. Reasons for exclusion included, early death (n=2) and incomplete data collection (n=2). Data analysis was performed in the remaining 26 patients.

Patient's characteristics were comparable as regard age, sex, GCS score at admission & discharge, and duration of stay in ICU without significant difference, as shown in table (I).Patients receiving Mg-lid combination showed statistically significant increase in serum ionized magnesium concentration at day 1, 2 and 3 when compared to the base line value as well as the control group (table II and fig(1).

Table I: Patient's characteristics. Data are expressed as mean ± SD (Range) or number (%).

Variable	Magnesium-Lidocaine group (n=26)	Control group (n=26)
Age (yr)	45.5 ± 16.2 (18-70)	41.6 ± 19.4 (20-68)
Sex (M / F)	24 / 2	21 / 5
Weight (Kg)	71 (63-78)	69 (60-75)
GCS score		
- At admission	4.3 ± 1.4 (3-7)	4.3 ± 1.1 (3-7)
- At discharge	7.1 ± 3.9 (3-13)	6.5 ± 3.8 (3-11)
Stay in ICU(day)	8.5 ± 5.7 (4-21)	7.2 ± 1.8 (3-26)

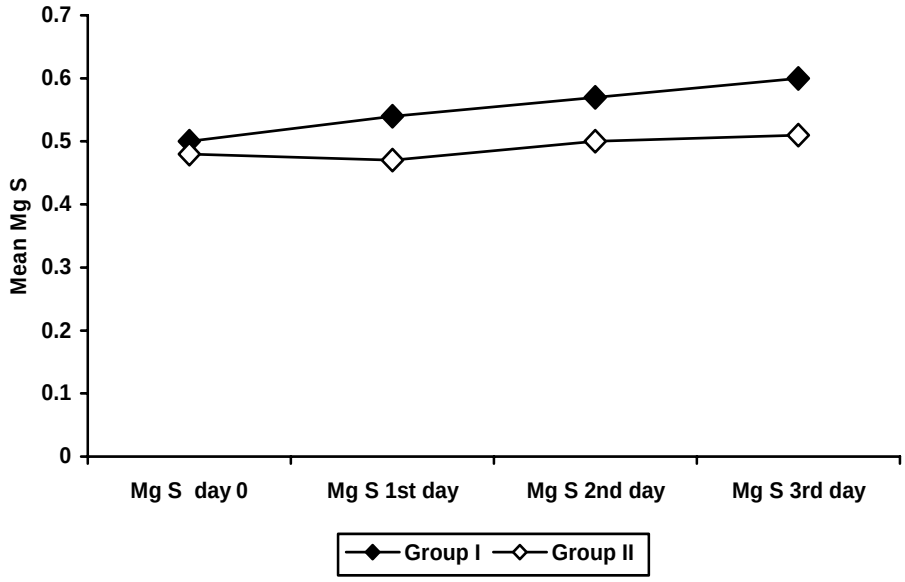

Fig 1. Mean Mg SO4 in both groups within 3 days.

As regard the mean values of blood sugar, admission samples were significantly decreased in all the subsequent samples. The other assessed parameters including Na^+, K^+, HCO_3, bilirubin, and serum creatinine at 1, 2, and 3 days were not changed from admission.

Regarding GOS, our results showed that in the control group after follow up for 6 months, there were 12 cases (46%) mortality, 1 case (4%) permanent vegetative state, 3 cases (12%) severe disability, 4 cases (15%) moderate disability, and 6 cases (23%) good recovery, while in the Mg-lid group, there were 7 cases (27%) mortality, 1 case (4%) permanent vegetative state, 4 case (15%) severe disability, 6 cases (23%) moderate disability, and 8 cases (31%) good recovery as shown in table (III).

Table II: Shows laboratory data in both groups. Data are expressed as mean ± SD.

Variable	Admission value	24hrs after admission	48hrs after admission	72hrs after admission	Normal values
Na (mmol/L)					
. Mg-lid group	137.2±6.2	142±6.2	143±7.2	142±5.4	137-146
. Control group	139.1±5.4	144±6.5	144±8.1	143±6.1	
K (mmol/L)					
. Mg-lid group	3.62±0.6	3.12±0.11	4.0±0.5	3.8±0.4	3.5-5.3
. Control group	3.54±0.5	3.51±0.10	3.6±0.52	3.5±0.71	
Ionized Mg (mmol/L)					
. Mg-lid group	0.50±0.02	0.54±0.04*†	0.57±0.05*†	0.60±0.02*†	0.44-0.59
. Control group	0.48±0.04	0.46±0.03	0.48±0.06	0.50±0.05	
HCO3 (meq/L)					
. Mg-lid group	22.8±1.7	24.6±2.8	25.2±3.1	23.3±2.8	≥ 20
. Control group	21.7±1.9	23.9±2.6	24.4±3.6	22.8±3.4	
Blood sugar (mg/dl)					
. Mg-lid group	189±38	155±36*	142±41*	132±24*	70-110
. Control group	186±40	162±38*	146±36*	135±26*	
Bilirubin (mg/dl)					
. Mg-lid group	1.2±0.3	1.2±0.5	1.3±0.5	1.2±0.4	<4
. Control group	1.1±0.4	1.4±0.3	1.3±0.5	1.2±0.6	
Creatinine(mg%)					
. Mg-lid group	0.95±0.65	0.97±0.03	1.05±0.34	1.03±0.50	0.70-0.31
. Control group	1.00±0.06	0.95±0.05	0.98±0.25	1.00±0.40	

*-*P < 0.05 = statistically significant compared to base line value.*
-†P < 0.05 = statistically significant compared to control group.

Table III: Shows Glasgow Outcome Score in both groups. Data are expressed as number (%).

	Number of cases	Good recovery		Moderate disability		Severe disability		Permanent vegetative state		Death	
		No.	%	No.	%	No.	%	No.	%	No.	%
Mg-lid group	26	8	31	6	23	4	15	1	4	7	27*
Controlgroup	26	6	23	4	15	3	12	1	4	12	46

*-*P < 0.05 = statistically significant compared to control group.*

DISCUSSION

The study was designed to evaluate the efficacy and safety of continuous intravenous infusion of magnesium sulfate and lidocaine over 3 days after severe head injury. The 3 days window was chosen on the basis of several studies showing this to be the critical period to deploy maximal neuroprotection[2,3,4].

This study demonstrates the safety and efficacy of usage of high dose magnesium in addition to lidocaine in SHI patients. In this study percentage of patients with favorable outcome was higher and the mortality rate was lower in comparison to literature results[1]. The findings of this study are consistent with Canavero et al.[8], who reported that a high dose magnesium and lidocaine after SHI is well tolerated in these patients and their clinical outcome compared favorably to the literature results.

Brain intracellular Mg^{++} is known to significantly decline following TBI for more than 12 hours. Administration of Mg^{++} salts following injury attenuates post-traumatic neurological deficits in animals due to both necrosis and apoptosis[7]. Moreover, hypermagnesemia vasodilates & counteracts early brain-associated vasoconstriction[1].

Magnesium is neuroprotective in animal models of trauma, focal brain ischemia, and subarachnoid hemorrhage[7,10]. Ischemia is the main aggravating factor after TBI and may stem from intracranial pressure (ICP) increase. Focal ischemia is common around hematomas. Moreover, biochemical damage in TBI and stroke follows similar patterns[2].

Magnesium exhibits a range of neuronal and vascular action that may ameliorate ischemic CNS insults, even when administration is delayed up to 6 hours after onset of insult. Magnesium levels decrease up to 60% a few minutes postinjury, with loss of endogenous antiglutamte potential[7,10].

Lidocaine infusion (IV, 3 mg/kg) triggers a 5-minute 10% reduction of cerebral O_2 consumption within 2 to 3 minutes. Lidocaine reduces in a dose dependent manner brain metabolism, suppresses synaptic transmission and stabilizes membranes by blocking pathologic K^+ efflux, Na^+ channels, and demand for Na^+-K^+ transport[7]. A double-blind 48 hours infusion of lidocaine at standard antiarrhythmic doses afforded cerebral protection during cardiac surgery[11].

In an experimental head injury model Bareyre showed the blood ionized Mg concentration to decline while the blood total Mg^{++} concentration remained constant[12]. Brain injury in rats results in an immediate and significant decline in total brain and intracellular ionized Mg^{++} concentration[13]. In clinical fields, Memon[14] reported that the serum ionized Mg decrease was related histologically and functionally to the severity of head injury based on CT scans demonstrating anatomic lesions, consciousness, or traumatic disturbances in the brain function. In our study the daily administration of magnesium significantly increased all subsequent serum magnesium values as compared with baseline values.

Although human studies have confirmed that moderate hypermagnesemia is well tolerated and feasible, only modest elevation of cerebrospinal fluid (CSF) [Mg^{++}] occurs. This modest increment of CSF [Mg^{++}] in brain-injured humans occurs in the range of 10 to 19%[15].

Mechanism of decrease of serum ionized Mg in head injury patients is still not understood. Catecholamines increase under such conditions in association with a lot of stress. Catecholamines promote lipid decomposition into fatty acids which then combine with Mg^{++}, resulting in decrease the ionized Mg concentration. Thus, ionized Mg accumulates in the fat cells. Both stress and rise of catecholamines levels increase the excretion of Mg in the urine[16]. These physiological changes may therefore decrease the ionized Mg concentration.

As regard the blood glucose level, this study together with other related studies demonstrated that admission hyper-glycemia is a frequent component of stress response to head injury[17]. The other assessment parameters such as serum Na^+, K^+, creatinine, HCO_3, and bilirubin were not significantly different.

There are several studies about the global outcome after severe traumatic brain injury, using the Glasgow Outcome Score either in its classic five grades or its modification as favorable & unfavorable.

Comparing our results with those of early researches at that field like as Becker et al.,[18], Jannette et al.[19], Miller et al.[20], we found that the mortality rate in our control group was 46%. This is nearly comparable to them 30%, 49%, and 40.5% respectively, which in the study group, our mortality rate markedly diminished to 27%, which was the lowest mortality rate in comparison to even the recent researches in that field as Rosner [21], which was 29% or even the Traumatic Coma Data Bank (TCDB) patients with a post resuscitation score of 7 or less in whom mortality rate was 40 %.

Percentage of patients having favorable outcome in the study group was 54 % versus 38 % in the control group and this is a significant difference. Even if some other researches registered comparable results in previous studies like Becker et al., (18) (58%), Rosner[21], (59%) because these studies were not comparative. At the same time, percentage of patients with favorable outcomes in the TCDB study was 37%, which is far less than our results after Mg sulfate and lidocaine administration[1].

The improved outcome which was observed in more recent studies had largely been attributed to minimizing or preventing cerebral ischemia by monitoring high cerebral perfusion pressure and general improvement in the critical care (Kelly et al., (22)). Miller et al.[23] examined the utility of GOS during early treatment (3 months) as a predictor of outcome of score 15 months post injury, and found that base line GOS was a reliable predictor of outcome in patients with initial score of 5 (no disability) or 4 (mild disability), but not in patients with an initial score of 3 (severe disability).

We concluded that a combination of magnesium and lidocaine is safe and well tolerated in patients with SHI. Patients in the magnesium lidocaine group showed a more favorable outcome and lower mortality rate when compared to the control group.

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