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Randomized controlled trial of magnesium sulphate in severe closed traumatic brain injury

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Abstract: Magnesium decline is likely to play an important role in the pathogenesis of Traumatic Brain Injury (TBI). This study was undertaken to test the therapeutic efficacy and safety of parenterally administered Magnesium sulphate ($MgSO_4$) in patients of severe closed TBI. Adult patients admitted within 12 hours of closed TBI with Glasgow coma score 5 to 8 fulfilling eligibility criteria were randomized to two groups, one group receiving 'standard care' and the other, $MgSO_4$ in addition as per the Pritchard regimen. The outcome measures were Glasgow outcome scale at 3 months and other relevant clinical parameters. Seventy patients were randomized after obtaining informed consent, and 30 in each group remained in the study till 3 months. Favorable outcome was observed in 22 out of 30 patients (73.3%) who had received $MgSO_4$, as compared with 12 out of 30 (40%) in control group. Univariate analysis revealed an odds ratio (OR) of 4.13 (95% CI 1.39-12.27) and the P value was 0.009. In the logistic regression analysis, the adj. OR was 4.24 (95% CI 1.1-16.36) and the P value was 0.036. The secondary outcomes analyzed in $MgSO_4$ group showed significant difference with respect to intra-operative brain swelling at the end of surgical decompression and mortality at 1 month. No significant adverse effects were observed. Parenteral $MgSO_4$ appears to have some favorable influence on mortality and intra-operative brain swelling without any significant adverse effects.

Keywords: Severe traumatic brain injury, Magnesium sulphate, Pritchard regimen, Outcome

Traumatic Brain Injury (TBI) is the most common cause of death and disability in young people[1]. There is no single pharmacotherapeutic agent that has shown efficacy in the treatment of clinical TBI[2]. However in the last two decades, it has become clear that the effects of the traumatic event are not instantaneous, but a substantial component of neuronal cell death resulting from the primary injury may begin many hours later[3]. Furthermore and most importantly, 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[6,7,8]. This study was undertaken to test the efficacy and safety of parenterally administered Magnesium sulphate ($MgSO_4$) in patients of severe closed traumatic brain injury.

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METHODS

Patients with TBI admitted to the Neurosurgery department at our institute from January to December 2004, fulfilling the following criteria were taken up for the trial.

INCLUSION CRITERIA

1. Closed TBI
2. Admission Glasgow coma score (GCS) 5,6,7 and 8
3. Age 18 to 60
4. Evaluated for randomization within 12 hours of injury.
5. Consenting guardian/ attendant

EXCLUSION CRITERIA

1. Hypotension (systolic BP ≤ 90 mmHg for ≥ 10 min)
2. Bilateral absent pupillary light reflex.
3. Extradural hematoma (> 5 mm thick on CT scan)
4. Known case of renal failure
5. Significant multisystem injury

6. Spinal injury

A computer generated randomization list was used and patients included in the trial were allocated to either of the two groups- one group receiving only 'standard care' and the other, $MgSO_4$ in addition.

Standard care consisted of ventilation, seizure prophylaxis with Phenytoin, antibitiotic prophylaxis with Netilmicin and Cefotaxime or Ceftriaxone, gastric ulcer prophylaxis with Ranitidine, and urinary catheterization done in all. Mannitol was given to patients with CT having evidence of focal mass effect or diffuse edema. Frusemide was added to patients with midline shift (>5 mm). Fluid and electrolyte homeostasis was maintained. Decision regarding ICP monitoring and surgical decompression was taken according to the mass effect noted in CT and was individualized to each patient. Patients allocated to $MgSO_4$ group received the same within 30 min of randomization as per the Pritchard regimen[9].

$MGSO_4$ REGIMEN BY PRITCHARD[9]

Formulation: 2 ml of 50% solution of $MgSO_4.7H_2O$ containing 1 gm of the same

Initiation: 4 gm $MgSO_4$ given IV as 20% soln. over 5-10 min, 5 gm $MgSO_4$ given IM as 50% soln. in upper outer quadrant of both buttocks through a 3 inch long 20 gauge needle (Total 14 gm)

Continuation: 5 gm $MgSO_4$ given IM as 50% soln. every 4 hourly till 24 hours after the first dose

$MgSO_4$ dose was withheld if

a) Urine output < 100 ml in 4 hrs
b) Blood urea > 50 gm/ dL
c) Fall of systolic BP < 90 mm Hg

Age, sex, regular alcohol intake, injury due to vehicular accidents, time since injury, BP, post-resuscitation admission GCS, admission urea and serum ionic magnesium (Mg^{2+}) levels (samples of 6 patients were not appropriate for Mg^{2+} evaluation due to hemolysis), Traumatic Coma Data Bank (TCDB) CT category[10] at admission, repeat CT findings after 6 hours and further upto discharge, urine output charting, details of surgical intervention, Intracranial pressure (ICP) recordings, clinical & laboratory parameters, and adverse events noted (any unwanted effect detected regardless of whether the effect could be attributed to the intervention) were entered in a pre-planned prospective database and were followed up till discharge or death.

OUTCOMES

The primary outcome was Glasgow outcome scale (GOS)[11] assessed at 3 months either directly or over telephone. Good recovery or moderate disability was considered as favorable and severe disability, persistent vegetative state or death was considered as unfavorable outcome. The secondary outcomes assessed were fresh development of mass effect in CT, mean intracranial pressure (ICP), intra-op brain swelling at the end of decompression necessitating duraplasty and/or bone flap removal, development of areas of infarction, prolonged ventilation, duration of hospitalization and mortality at 1 month.

STATISTICAL ANALYSES

All analyses followed on-treatment principle. Patients who were lost to follow-up were excluded from the analyses. SPSS 10 software (SPSS Inc,USA) was used for the statistical analyses. Proportions were compared by using chi-square tests or Fisher's exact test wherever appropriate. Continuous variables were compared by using independent-samples T test. Subgroup analyses were done using Breslow-Day test of homogeneity of odds ratios. Multivariate analyses were conducted with logistic regression adjusting for well known prognostic factors such as age, GCS, and TCDB category. Two sided significance tests were used throughout, and the significance level was kept at p=0.05.

RESULTS

Seventy patients admitted during the study period who fulfilled the eligibility criteria were randomized to two groups of 35 each for the trial (Fig 1). In the test group, one did not receive $MgSO_4$ due to hypotension, another due to oliguria and three others were lost to follow-up. In the control group, five patients were lost to follow-up. The final study population consisted of 60 patients, with 30 in each group.

There were no significant differences between the groups in demographic characteristics or injury severity at baseline (Table 1).

OUTCOMES

Primary outcome

Favorable outcome of good recovery or moderate

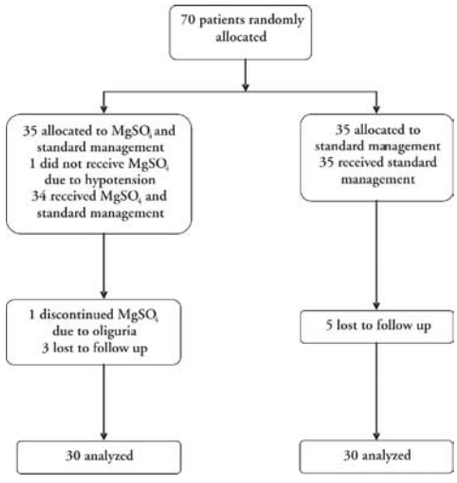

Fig 1: Trial flow diagram

Table1: Baseline characteristics

Characteristic		Control (n=30)	$MgSO_4$ (n=30)	*p* value
Mean age in yrs (SD)		37.6 (±12.9)	33.6 (±10.6)	0.20
No. of women		6 (20%)	1 (3.3%)	0.10
Regular alcohol intake		6 (20%)	8 (26.7%)	0.54
No. of vehicular accidents		26 (86.7%)	30 (100%)	0.11
Trial entry interval	n ≤ 6 hrs	19 (63.3%)	17 (56.7%)	0.60
	Mean value hrs (SD)	5.5 (±3.3)	6.7 (±3.4)	0.15
GCS	5	8 (26.7%)	5 (16.7%)	0.71
	6	6 (20%)	5 (16.7%)	
	7	9 (30%)	10 (33.3%)	
	8	7 (23.3%)	10 (33.3%)	
Motor score of GCS	3	9 (30%)	6 (20%)	0.19
	4	9 (30%)	5 (16.7%)	
	5	12 (40%)	19 (63.3%)	
TCDB CT category	I	1 (3.3%)	0 (0%)	0.47
	II	9 (30%)	12 (40%)	
	III	9 (30%)	7 (23.3%)	
	IV	5 (16.7%)	2 (6.7%)	
	Mass lesion > 25 cc (V)	6 (20%)	9 (30%)	
CT status of cisterns	TCDB I, II	10 (33.3%)	12 (40%)	0.59
	III, IV, V	20 (66.7%)	18 (60%)	
Mean admission serum ionic Mg^{2+} in mmol/L		0.37 (±0.06)	0.38 (±0.05)	0.51
No. underwent surgical decompression		15 (50%)	17 (56.7%)	0.61

disability at 3 months was observed in 22 out of 30 patients (73.3%) who had received $MgSO_4$, as compared with 12 out of 30 (40%) in control group (Fig 2). The odds ratio (OR) was 4.13 (95% Confidence interval 1.39-12.27) and the *p* value was 0.009. Good recovery was seen in 14 out of 30 (46.7%) in $MgSO_4$ group as compared with 6 out of 30 (20%) in control group. The OR was 3.5 (95% CI 1.11-11.02) and the *p* value was 0.028. Both were statistically significant. The number of patients dead, in persistent vegetative state, with severe disability and moderate disability were 14 & 4, 2 & 0, 2 & 4, 6 & 8 in control and $MgSO_4$ groups respectively (Fig 2).

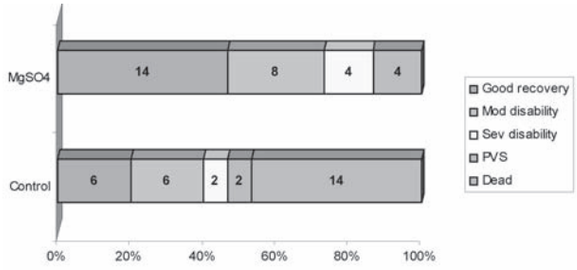

Fig 2: Primary outcome (GOS) at 3 months

Secondary outcomes

In patients belonging to TCDB CT category I to IV, 5 out of 21 in $MgSO_4$ group and 3 out of 24 in control group had worsening of mass effect in the form of progression to higher category in CT repeated after 6 hours. It was not statistically significant (OR 2.2, *p*= 0.44). The mean of ICP recordings performed in 3 non-surgical patients each in either group was 7.67(±2.1) and 8.00(±1.0) mm Hg respectively and was not statistically significant (Mean difference -0.33, *p*=0.82).

Among those in TCDB III-V, surgical decompression was done for 17 and 15 patients in $MgSO_4$ and control groups respectively. Small frontal contusion & normal ICP was noted in 1 and 2 patients in $MgSO_4$ and control groups, and 3 in control group had small frontal contusions with diffuse edema and were therefore managed conservatively. Significant intra-operative brain swelling at the end of the surgery was noted in 5 out of 17 (29.4%) and 11 out of 15 (73.3%) patients in $MgSO_4$ and control groups respectively, which was statistically significant (OR 0.15, *p*=0.01).

Development of areas of infarction was seen in 2 and 6 patients in $MgSO_4$ and control groups respectively. Prolonged ventilation (> 7 days) was noted in 18 out of 30 and 16 out of 23 patients surviving more than 7 days in $MgSO_4$ and control groups respectively. The mean duration of hospitalization for patients alive was 23.1 and 23.5 days in $MgSO_4$ and control groups respectively.

None of the above was significant.

The number of patients dead at 1 month was 4 (13.3%) and 13 (43.3%) in $MgSO_4$ and control groups respectively, which was statistically significant (OR 0.2, p=0.01).

Table 2: Secondary outcomes

Secondary outcomes		Control	$MgSO_4$	OR/Difference* (95% CI)	p value
Categorical	Fresh development of mass effect in CT	3/ 24 (12.5%)	5/ 21 (23.8%)	2.2 (0.45-10.54)	0.44
	Intra-op brain swelling	11/15 (73.3%)	5/ 17 (29.4%)	0.15 (0.03-0.71)	0.01
	Areas of infarction	6 (20%)	2 (6.7%)	0.29 (0.05-1.55)	0.25
	Ventilation > 7d	16/23 (69.6%)	18/ 30 (60%)	0.66 (0.21-2.07)	0.47
	Mortality < 1 mth	13 (43.3%)	4 (13.3%)	0.2 (0.06-0.72)	0.01
Continuous*	Mean ICP mm Hg (SD) in non-surgical pts	8 (±1)	7.67 (±2.1)	-0.33 (-4 to 3.4)	z.82
	Mean duration of hospitalization in days (SD) for patients alive	21.13 (±11.9)	23.54 (±22)	2.41(-9.7to14.5)	0.69

Table 3: Subgroup analyses

Subgroups			Good recovery or moderate disability		OR (95%CI)	p value*
			Control	$MgSO_4$		
A priori	CT category	I, II	6/ 10 (60%)	9/ 12 (75%)	2 (0.3-12.3)	0.34
		III, IV, V	6/ 20 (30%)	13/ 18 (72.2%)	6.1 (1.5-24.8)	
	Trial entry	< 6 hrs	11/ 19 (57.9%)	14/ 17 (82.4%)	3.4 (0.7-15.9)	0.27
		> 6 hrs	1/ 11 (9.1%)	8/ 13 (61.5%)	16 (1.5-166)	
	Therapy	Non-surgical	6/ 15 (40%)	10/ 13 (76.9%)	5 (1-26.1)	0.77
		Surgical	6/ 15 (40%)	12/ 17 (70.6%)	3.6 (0.8-15.6)	
Post-hoc	GCS	5, 6	4/ 14 (28.6%)	8/ 10 (80%)	10 (1.4-69.3)	0.23
		7, 8	8/ 16 (50%)	14/ 20 (70%)	2.3 (0.6-9.2)	
	Admission serum ionic Mg^{2+}	< 0.4 mmol/L	8/ 18 (44.4%)	14/ 19 (73.7%)	3.5 (0.9-13.9)	0.65
		≥ 0.4 mmol/L	4/ 8 (50%)	6/ 9 (66.7%)	2 (0.3-14.2)	

* Breslow-Day test of homogeneity of OR

The effect of $MgSO_4$ in improving outcome in various subgroups of patients categorized apriori on the basis of CT category, trial entry interval, surgical decompression and post-hoc on the basis of GCS, and admission serum ionic Mg^{2+} levels did not reveal any significant subgroup difference (Table 3).

Adjusting for well known prognostic factors such as age, GCS, effacement of cisterns in CT (TCDB III-V), and also early trial entry (<6 hrs), low admission serum ionic Mg^{2+} (<0.4 mmol/L), the logistic regression model was found to be significant (p<0.05) with respect to the following outcome parameters- good recovery, good recovery or moderate disability, absence of intra-operative brain swelling and mortality at 1 month (Fig 3). Among the other factors, significant association was found between early trial entry with good recovery or moderate disability (Adj. OR 8.2, p=0.008) and CT finding of uneffaced cisterns (TCDB I, II) with good recovery (Adj. OR 4.67, p=0.04).

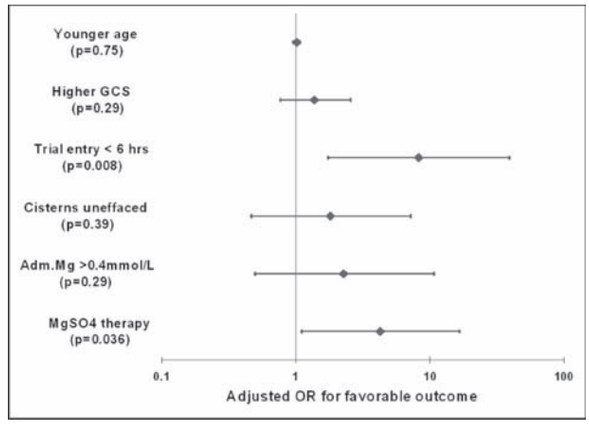

Fig 3: Logistic regression

In the control group, 9 patients died of neurological deterioration, 2 due to pneumonia, 2 due to renal failure, and 1 due to septicemia. In the $MgSO_4$ group, 3 patients died of neurological deterioration and 1 due to pneumonia. The adverse events noted in $MgSO_4$ and control groups were as noted (Table 4).

Table 4: Adverse events

Advers e event	Control	$MgSO_4$	
< 1 month	Renal failure	2	1
	Hypotension	2	3
	Seizures	2	3
	Pneumonia	8	7
	Coagulopathy	3	1
	Meningitis	4	6
> 1 month	Hydrocephalus	0	2

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[12]. Unfortunately the clinical trials that have attempted to inhibit individual secondary factors[1,2,3]- lipid peroxidation (steroids and Tirilizad), free radical injury (Superoxide dismutase), calcium influx (Nimodipine), glutamate

excitotoxicity (Selfotel), apoptosis (Cyclosporine A), and edema (substance P antagonists) have met with very limited success due to the heterogeneous nature of secondary injury[13] that includes secondary mass lesions and edema,[1] secondary ischemic brain damage[14] and secondary axonal injury[3].

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[15].

It affects a number of secondary injury factors[5], the most predominant action in animal models being on NMDA excitotoxicity either by receptor blockade[16], or by decreasing glutamate release[17]. The other neuroprotective mechanisms proposed are calcium channel antagonism[18], maintenance of cerebral blood flow[19], apoptosis prevention[2], and â amyloid precursor protein upregulation[3].

Vink et al demonstrated 70% decline of intracellular free Mg^{2+} in the cortex of brain-injured rats, using ^{31}P MRS, within the first hour of injury and non-recovery of the same over the next 3 hours[20]. They later demonstrated its correlation with functional outcome[21]. In a small group of patients with severe TBI, plasma total Mg was found to be low[22]. Parallel decrease in free ionized Mg^{2+} has been found in animal[23] and human[24] studies which correlated with the outcome[23] and severity[24]. This is most likely due to enhanced glucose metabolism by glycolysis[25, 26] and can also be due to urinary losses[22]. 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[27].

Administration of Mg salts after experimental TBI was found to improve neurological outcome[6-8], both with respect to motor[7] and cognitive performance[8]. It was also noted that Mg treatment significantly reduced the volume of cortical histological lesion following experimental TBI in rats[28]. Heath et al demonstrated a potential therapeutic window of 24 hours after trauma in rats[29]. In their experiments, Mg therapy significantly improved motor outcome when administered upto 24 hours after injury with earlier administration resulting in more pronounced improvement. Repeated administration beyond 24 hours did not further improve outcome[29].

Our results show a significant association of $MgSO_4$ with favorable outcome (Fig 3), as previously seen in experimental studies[6,7,8]. The only other parameter showing significant association with $MgSO_4$ was intra-operative brain swelling known to be caused predominantly by cytotoxic edema[30,31] due to Glutamate activated NMDA receptor mediated Ca^{2+} influx on which Mg acts[32]. Areas of infarction were 3.4 times less frequent in the $MgSO_4$ group (Table 2). Though statistically not significant, probably due to the small number of patients in our trial, it may be clinically relevant considering the importance of ischemia in secondary injury[1,14,30], and the proven efficacy of $MgSO_4$ in delayed cerebral ischemia of SAH[33]. Among patients of TCDB CT category I & II, the odds ratio of favorable outcome in $MgSO_4$ group was 2 times the control (Tab 3). Though not significant, this may reflect the possible role of Mg in attenuation of secondary axotomy[3]. These three neuroprotective effects may have acted together in improving outcome and reducing mortality in the $MgSO_4$ group in our study.

Though the Pritchard regimen[9] of $MgSO_4$ has been in vogue for eclampsia since 1955, a series of trials by Lucas et al[34] and the Magpie trial collaborative group[35] have clearly demonstrated its efficacy only in the last decade, possibly due to its vasodilator effect[36] on eclamptic vasospasm[37]. The largest study till date- the Magpie trial[35] done on 10,141 pregnant women with 5,071 receiving $MgSO_4$ revealed no significant adverse reactions.

Canavero et al, in a non-controlled study on 32 patients of severe head injury who received parenteral $MgSO_4$, noticed lower mortality at 6 months (12.5%) [38] as compared to other published literature (45-55%)[39]. Based on the study demonstrating equivalent efficacy of intravenous and intramuscular regimens, we have used maintenance intramuscular regimen[40]. Placebo was not given in the control group considering the neurological status of patients. Considering the absence of blinding and therefore a possible assessment bias, a larger multicentre double-blinded randomized controlled trial with long-term outcome, is needed to confirm the findings of the present study. A larger study may also reveal additional significant factors, which have not emerged so in our study given the modest sample size. Because of its low price, well-established safety profile[35] and critical physiological role[5], $MgSO_4$ may emerge as a valuable

neuroprotective agent in the therapy of TBI.

CONCLUSION

Parenteral Magnesium sulphate appears to reduce mortality, intra-operative brain swelling, and has favorable influence on outcome 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.

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