

## Loading dose versus standard regimen of magnesium sulphate in eclampsia – a randomized trial

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### ABSTRACT

Eclampsia is one of the leading causes of maternal mortality and morbidity around the world. Magnesium sulphate is used as primary agent in the treatment of seizure in eclampsia. Its dosage and frequent painful injection makes it a difficult drug for the patient. This study was carried out in one of the biggest referral centre of Nepal to study the suitability of different dosage schedule for our patient. A randomized controlled trial was carried out in the Obstetric Unit of BP Koirala Institute of Health Science (BPKIHS) over the span of 1.5 years. A total of 80 eclamptic women were randomized to receive either standard Pritchard Regimen (loading and maintenance) or Loading dose of magnesium sulphate. Both groups were evaluated for recurrence of seizures and outcomes. There were no recurrent seizures in standard regimen group. There were 2 patients with recurrent seizure in loading dose group. ( $p=0.184$ ) Loading dose of magnesium sulphate is a good alternative for standard Pritchard regimen. It avoids multiple painful injections of magnesium Sulphate.

**Keywords:** Eclampsia, magnesium sulphate, recurrent convulsions.

### INTRODUCTION

Eclampsia was initially recognized centuries ago in ancient Egypt as seizures occurring uniquely in the context of pregnancy, as they resolved with delivery. Currently, the incidence of eclampsia is estimated at a rate of 0.04% to 0.1% in the United States and United Kingdom.<sup>1,2</sup> In contrast, it is much higher in developing countries, with reported rates as great as 15.0%.<sup>3</sup> It is estimated that eclampsia is a factor in up to 10.0% of all maternal deaths in developed countries and accounts for around 50,000 maternal deaths per year worldwide.<sup>4,5</sup>

Eclampsia is a multi-system disorder with complex pathogenesis, which is not completely understood. Cerebral involvement causing convulsions can kill the mother and fetus unless expertly managed. Over the centuries, many diverse therapies have been employed (rightly or wrongly) to both prevent and cure this condition. These include systemic (sedation with morphine and chloral hydrate, phlebotomy, gastric lavage, mastectomy, and renal decapsulation) as well as hormonal (oophorectomy) and neuronal (spinal tap) interventions.<sup>6</sup> Among the many anticonvulsants, magnesium sulfate ( $MgSO_4$ ) topped the list for treatment of convulsion.<sup>7</sup> Today  $MgSO_4$  has been used to treat eclampsia for over 75 years and it is broadly accepted as a reliable means for preventing eclampsia.

Magnesium sulphate is widely used nowadays for prophylaxis in severe preeclampsia as well as treatment of seizures in eclampsia. Pritchard recommends giving

4 g  $MgSO_4$  intravenously over 5 minutes, followed immediately by 10 g intramuscularly and 5 g intramuscularly every 4 hours.<sup>8</sup> Zuspan promotes a 4-g intravenous loading dose over 15 minutes followed by a 2- to 3-g/hr maintenance infusion.<sup>9,10</sup>

In Dhaka Medical College Hospital (DMCH), according to guidelines published by the Eclampsia Working Group, the dose schedule is 4g intravenous and 3g intramuscular injection in each buttock as a loading dose followed by 2.5g intramuscularly every 4h in each alternate buttock until 24 h after delivery or the last fit.<sup>11</sup>

It has recently been suggested that an initial loading dose of  $MgSO_4$  is sufficient to arrest convulsion.<sup>12</sup> We also observed that most of the patients did not receive maintenance therapy due to suspicion of toxicity and they did not convulse further. On the basis of these observations a pilot study was done to compare the efficacy of loading and the standard regime. After getting satisfactory results from the pilot study this randomized trial was undertaken to compare loading and standard regimes for eclampsia and to observe the result in terms of recurrent convulsions.

### MATERIALS AND METHODS

This randomized trial was undertaken at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal between 2008 July- 2009 December after obtaining institutional ethical approval. All the women who had eclampsia (ante partum and post partum) were included

**Table-1:** Patient profile between standard dose regime (Group A) and loading dose regime (Group B)

SN	Characteristics	Group A (n=37)	Group B (n=43)	Significance
1	Age (in years)	21.57±4.15	20.98±3.31	not significant (p=0.710)
2	Parity	<1	<1	not significant (p=0.240)
3	Type of Eclampsia			
a	Antepartum	33	36	not significant (p=0.431)
b	Postpartum	4	7	not significant (p=0.332)
4	Gestational age (weeks)	35.42±3.78	37.03±2.41	not significant (p=0.212)

**Table-2:** Comparison of disease severity between two groups

SN	Parameters	Group A (n=37)	Group B (n=43)	Significance
1	No of convulsion	7.62±5.36	5.93±4.76	not significant (p=0.084)
2	Glasgow Coma Scale	10.89±4.20	11.88±3.57	not significant (p=0.067)
3	Seizure to MgSO <sub>4</sub> (hours)	11.24±16.51	7.42±7.49	Significant (p=0.046)
4	Systemic Effects			
a	Abnormal LFT	9	6	not Significant (p=0.139)
b	Abnormal RFT	12	8	not Significant (p=0.236)

LFT= Liver function test, RFT=Renal function test

in the study. The women who received magnesium sulphate outside our hospital were excluded from the study. After standard loading dose, patients were randomized by block randomization to Group A (loading and maintenance dose) or Group B (loading dose only). They were followed up for recurrent convulsions. In event of recurrent convulsions, further 2 gm of magnesium sulphate was given intravenous and maintenance regimen continued as usual. In Group B, when patient had recurrent seizures they were switched to maintenance protocol. The patients were followed up till the discharge from the obstetric unit of the hospital. Any complications and need of intensive care were noted.

The results were analyzed using SPSS 13 version. Level of significance was determined using Pearson's Chi

**Table-3:** Patient outcome after treatment

SN	Parameters	Group A (n=37)	Group B (n=43)	Significance
1	MgSO <sub>4</sub> - Delivery Interval	4.36±3.5	6.22±7.83	(p=0.81) not Significant
2	Recurrent Seizures	0	2	(p=0.184) not significant
3	Outcome (Death)	0	1	P=0.351) not significant
4	Duration of stay (in days)	7.19±6.52	6.72±5.74	(p=0.531) not significant
5	Need of ICU care	9 (32%)	6 (16%)	(p=0.236) not significant

Square Test. P valued ≤0.05 was considered significant.

## RESULTS

There were total of 125 cases of eclampsia in the study duration. There were total 10512 deliveries in the study duration. So the incidence of eclampsia was 1.2%. Among 125 eclamptic 45 were excluded from the study because they received magnesium sulphate outside. Total of 80 women were randomized to receive either standard Pritchard regime (Group A, n=37) or to loading dose only (Group B, n=43).

The profile of the patients between category A and Category B were comparable. The mean age of the patients were 21.57±4.15 years and 20.98±3.31 years respectively. There were no significant differences in parity and gestational age of the patients between two groups (Table-1).

The disease severity indicators between the two groups were also comparable (Table-2). The numbers of convulsions between two groups were 7.62±5.36 and 5.93±4.26 respectively. There was no significant

difference in Glasgow Coma Scale (GCS), systemic effects (in the form of abnormal liver function test and renal function test) between the two groups. However, duration between onset of seizure and Magnesium Sulphate injection was significant between two groups.

There was no significant difference in the recurrent seizure after magnesium sulphate between two groups (Table-3). Group A patients did not have any recurrent seizures where as 2 patients in Group B had recurrent seizures. There was single maternal death in group B. 32.0% patients in Group A and 16.0% patients in Group B needed intensive care. The average duration of hospital stay was about a week in both groups. Almost all the patients needed antihypertensive at the time of discharge from hospital.

The rate of cesarean delivery was higher in Group B, 50.0% patients underwent cesarean section. Almost all the women whose fetus were viable and Bishop Score unfavorable at the time of presentation had cesarean section in both groups. The weight of the baby in both groups was also comparable (Table-4).

## DISCUSSION

Magnesium sulphate is superior to all other anticonvulsants in controlling and preventing seizures in preeclampsia and eclampsia.<sup>13</sup> Two

Table-4: Pregnancy outcome

SN	Parameter	Group A	Group B	Significance
1	Mode of Delivery			
a	Vaginal	24	23	not Significant (p=0.333)
b	LSCS	13	20	not Significant (p=0.422)
2	Weight of Baby (in kilograms)	2.19±0.72	2.45±0.70	not Significant (p=0.579)

most common regimens used are combined intravenous and intramuscular regime, as advised by Pritchard,<sup>8</sup> and continuous intravenous regime as advised by Zuspan.<sup>9</sup> <sup>10</sup>In our study, intramuscular regime was used according to National guidelines of our country.

Though magnesium sulphate is being used widely, in many occasions seizures recur. In a study conducted at Dhaka medical college hospital by Mosammat Rasida Begum, recurrent seizures were 4.0% in loading dose group and 3.5% in standard regime group.<sup>11</sup> The result of the collaborative eclampsia Trial shows recurrent convulsion rate 13.2% (60/453) and 5.7% (22/388) in two controlled trials.<sup>7</sup> The recurrent convulsions in our study was 4.6% in loading dose only group, there were no convulsions in standard regimen group. It is comparable to both of the trials above. One of the patients who had recurrent seizures in our study was later on diagnosed as meningoencephalitis, so probably eclampsia was not the cause of the recurrence. There has been always paucity in recurrent seizures while on magnesium sulphate in our experience. Phuapradit *et al.* found that mean serum magnesium levels were significantly lower in women having a weight >70kg than the level observed in patients with a body weight <70kg.<sup>14</sup> After a loading dose, the drug is distributed throughout the body especially in skeletal tissue and only a small amount is left in the extra cellular fluid. Since lighter patients have a lower total body volume the drug concentration is accordingly higher in serum during the treatment with the maintenance regime.<sup>15-17</sup> Sibai and Ramanathan found that about 10.0% of eclamptics experience a further convulsion after receiving a loading dose of MgSO<sub>4</sub>.<sup>18</sup> This was much greater than seen in our study. The study evaluated western women. Since our patients have lesser body weight, the recurrent seizures are probably less.

The maternal mortality in our study was low. There was only one death in loading dose only group (2.3%) as compared to study in Dhaka where it was 4.5% in study group and 5.0% in control group.<sup>11</sup> The Eclampsia Trial Collaborative Group showed a reduction in the risk of recurrent seizures of 52.0% and 62.0% with MgSO<sub>4</sub>

compared with diazepam and phenytoin. But the reduction of seizure rates did not affect maternal mortality rates. Magnesium Sulfate was associated with a significant reduction in the number of seizures without any effect on maternal mortality or morbidity.<sup>7</sup> As eclampsia is a multiorgan disorder, mortality depends on the severity of the organ damage. So loading or maintenance schedule probably had no effect on mortality.

The present study suggested that loading dose of magnesium sulphate is as effective as standard regimen in controlling seizures in eclampsia. The recurrent seizure rate was comparable in both group. Providing only loading dose to the patients reduces painful intramuscular injections and also definitely reduces the cost. So, loading dose only regimen is suitable for our group of patients.

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#### REFERENCES

- Coppage KH, Sibai BM. Hypertensive Emergencies in Obstetric Intensive Care Manual. 2nd ed. New York, NY: McGraw- Hill; 2004.
- Walker JJ. Severe preeclampsia and eclampsia. *Balliere's Best Pract Res Clin Obstet Gynaecol* 2000; 14: 57-71.
- Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Brit J Obstet Gynaecol* 1992; 99: 547-53.
- Douglas KA, Redman CWG. Eclampsia in the United Kingdom. *Brit Med J* 1994; 309: 1395-400.
- World Health Organization International collaborative study of hypertensive disorders of pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *Amer J Obstet Gynecol* 1988; 158: 80-83. A population based study. *Brit Med J* 1998; 316: 1343-7.
- Zuspan FP. Problems encountered in the treatment of pregnancy-induced hypertension. *Amer J Obstet Gynecol* 1978; 131: 591-7.
- The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; 345: 1455-63.
- Pritchard JA. The use of the magnesium ion in the management of eclampogenic toxemias. *Surg Gynecol Obstet* 1955; 100: 131-40.
- Zuspan FP. Treatment of severe preeclampsia and eclampsia. *Clin Obstet Gynecol* 1966; 9: 954-72
- Sibai BM, Graham JM, McCubbin JH. A comparison of intravenous and intramuscular magnesium sulfate regimens in pre- eclampsia. *Amer J Obstet Gynecol* 1984; 150: 728-33.
- Begum MR, Begum A, Quadir E. Loading dose versus standard regime of magnesium sulfate in the management of eclampsia: A randomized trial. *J Obstet Gynaecol Res* 2002; 28: 154-9.

12. Boyd C, Brower G. (eds) Practical Guide to High Risk Pregnancy and Delivery. Singapore: Harcourt Brace Asia, 1993.
13. Chien PF, Khan KS, Arnott N *et al*. Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: An overview of the evidence from randomized trials. *Brit J Obstet Gynaecol* 1996; 103: 1085-91.
14. Phuapradit W, Saropala N, Haruvasin S, Thuvafethakul PTS. Serum level of magnesium attained in magnesium sulphate therapy for severe pre-eclampsia. *Asia-Oceania J Obstet Gynecol* 1993; 19: 387-90.
15. Brandt JL, Glaser W, Jones A. Soft tissue distribution and plasma disappearance of intravenously administered isotopic magnesium with observations on uptake in bone. *Metabolism* 1958; 7: 355-62.
16. Chesley LC. Parenteral magnesium sulphate and the distribution, plasma levels and excretion of magnesium. *Amer J Obstet Gynecol* 1979; 133: 1-7.
17. Chesley LC, Tepper I. Plasma level of magnesium attained in magnesium sulphate therapy for preeclampsia and eclampsia. *Surg Clin North Amer* 1957; 37: 353-66.
18. Sibai BM, Ramanathan J. The case for magnesium sulphate in preeclampsia. *Int'l J Obstet Anesth* 1992; 1: 167-75.