

Making Magnesium Sulfate Therapy Safer in Eclampsia: A Comparative Study of Zuspan Regime vs Low-dose Intravenous MgSO₄ Regime

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ABSTRACT

Objective: Magnesium sulfate is a universally accepted drug for the control of convulsions in eclampsia. Regimes available have been well tried in western countries where the weight of women is much higher than Indian women. In the present study, we tried to compare the doses used in zuspan regime (used previously in our hospital) with the regime where we reduced the maintenance dose to half for average weight women of the rural area (≤ 50 kg).

Design: A PRE-POST comparative study of 2 regimes of magnesium sulfate therapy in cases of eclampsia.

Setting: Tertiary care center in the low-resource rural area of central Gujarat.

Population: Group I: All patients of eclampsia, March 2007 to April 2012. Group II: All patients with eclampsia who were weighing ≤ 50 kg (BMI ≤ 25) May 2012–Oct 2013.

Materials and methods: Group I: Zuspan regime: Loading dose 4 g intravenously 20% over 20 minutes and maintenance dose 1 g/hour intravenously. Group II: Low maintenance dose regime: Loading dose: 4 g intravenously 20% over 20 minutes and maintenance dose: 0.5 g/hour.

Main outcome measures: Rates of recurrence of convulsions, magnesium sulfate toxicity, and maternal mortality.

Results: Recurrent convulsion rate was 5% in group I and 9.6% in group II. Toxicity was seen in 15.3% of cases in group I while it was not seen in group II. Maternal mortality in group I was 1.5% and no mortality in group II.

Conclusion: A low maintenance dose of magnesium sulfate is safe and effective for controlling convulsions in patients with eclampsia weighing ≤ 50 kg.

Keywords: Eclampsia, Low maintenance dose regime, Magnesium sulfate, Maternal mortality, Zuspan regime.

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INTRODUCTION

Eclampsia is an extremely severe form of preeclampsia characterized by sudden onset of generalized tonic-clonic seizures responsible for 17–30% maternal mortality and 22% perinatal mortality.¹

The incidence of eclampsia in developed countries is around 1.610 cases per 10,000 deliveries while it is 6–157 per 10,000 deliveries in developing world.² The mortality rates also vary widely 5–15%. The incidence of eclampsia in India as per Eclampsia Registry³ is 41/10,000 deliveries, and mortality is around 1% cases of eclampsia.

Eclamptic convulsions are life-threatening emergencies and carry a risk of high morbidity and mortality if not managed timely and appropriately. Amongst the principles of management of eclampsia, the first and foremost is the control of convulsions. Magnesium sulfate is the gold standard for anticonvulsant action in the treatment of eclampsia. Eclampsia collaborative trial 1995 demonstrated that magnesium sulfate is the drug of choice for eclampsia and reduced the risk of recurrent convulsion and maternal mortality.⁴ Cochrane review also confirms the same.^{5–8} Up till now a majority of studies of magnesium sulfate therapy like Pritchard, Zuspan, and Sibai have been carried out in western countries where the weight of a woman is much higher than Indian women.^{9–11}

It is important to find out a minimum effective dose in women having average weight (≤ 50 kg) in rural Gujarat so that to minimize magnesium sulfate toxicity. Similarly, Bhattacharjee et al. have

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demonstrated that we can reduce the total MgSO₄ requirements with an increased safety margin.¹² The present study was designed to compare efficacy and safety of zuspan regime which was previously used for many years in our institute with the outcome of patients who have received the further low maintenance dose of average weight women (≤ 50 kg) of rural area.

MATERIALS AND METHODS

The present study was conducted at a tertiary care center in the rural area of central Gujarat, India. The study was carried out in 50 bedded

medical-surgical ICU (intensive care unit)/HDU (high dependency unit) in a 550 bedded, university-affiliated trust hospital and rural medical college in central Gujarat, India. The hospital provides antenatal care to 1600 patients annually of which 70% constitute high-risk pregnancies. The institution has the availability of the services of an obstetrician, neonatologist and intensivist round the clock. The incidence of eclampsia at our institute is around 403/10,000 obstetric admissions as our institute is a tertiary care center. The mortality of eclampsia at our institute is 10.4% of overall maternal death, mortality among all eclampsia pt is 4.6%. 15–20% of eclampsia patients were serious enough to require ICU admission for ventilator support.

The study was reviewed and approved by the Institutional Human Research Ethics Committee and permission was granted to start the same. The study was conducted under two subgroups.

- Group I consisted of the retrospective observational study of the maternal and fetal outcome of eclampsia patients who received zupspan regime. The study period was from March 2007 to April 2012 (5 years). Consecutive cases files were procured from the Medical Record Department of the hospital. Data were recorded in a proforma.
- Zupspan regime: Loading dose 4 g magnesium sulfate intravenously 20% over 20 minutes and maintenance dose 1 g/hour intravenously in infusion pump till 24 hours of delivery or last seizure whichever is later. If seizure reoccurred, then magnesium sulfate 2 g 20% intravenous was repeated additionally and maintenance dose was increased from 1 g/hour to 1.5 g or 2 g/hour.
- Group II was prospective interventional study carried out from May 2012 to October 2013 by giving low maintenance dose (IV—0.5 g/hour) after loading dose 4 g magnesium sulfate intravenously 20% over 20 minutes, in the treatment of eclampsia cases who were weighing around 50 kg.

Inclusion Criteria

- Group I: All patients with eclampsia. Group II—All patients with eclampsia who were weighing around 50 kg.

Exclusion Criteria

- Group I: Pregnancy with other causes of seizures were excluded such as the known case of epilepsy.
- Group II: Pregnancy with a known case of epilepsy; and complicated eclampsia like status eclampticus and systemic involvement.

Patient weighing >50 kg.

Eclampsia was diagnosed that seizures that cannot be attributed to other causes in women with preeclampsia. As per Guideline from Working Group Report On High Blood Pressure during Pregnancy if systolic blood pressure is >140 mm Hg, while diastolic BP is >90 mm Hg, along with proteinuria Preeclampsia was considered severe when systolic BP >160 and diastolic BP >110 mm Hg.¹³

All the cases were admitted to either high dependency unit or ICU, detailed history and clinical examination was done and basic investigations were sent. The main aim was to prevent further convulsions, to control hypertension, and to stabilize the patient.

Low Maintenance Dose Regime

Loading dose—4 g magnesium sulfate intravenously 20% over 20 minutes and maintenance dose: 0.5 g/hour intravenously in

infusion pump until 24 hours of after delivery or after the last seizure. If seizure recurred, then magnesium sulfate 2 g 20% intravenous repeated and maintenance dose was changed from low dose 0.5 to 1 g/hour.

Blood samples were withdrawn for estimation of serum magnesium level; first within 30 minutes of starting magnesium sulfate therapy, and thereafter every 4 hours for total 3 such samples.

Toxicity

It was diagnosed when deep tendon jerks disappear, the respiratory rate falls below 12 per minutes or cardiac arrhythmia occurs. The decision for discontinuation of magnesium sulfate infusion was taken when any sign of magnesium sulfate toxicity appeared, or urine output fell below 30 mL per hour.

Injection of calcium gluconate 10%, 10 mL was given in a case of detection of magnesium sulfate toxicity.¹⁴

Antihypertensives (like labetalol, nifedipine or nitroglycerine drip) were used to control severe hypertension and were administered to keep diastolic blood pressure at around 90 mm Hg.

Obstetric management was carried out after stabilizing the patient, as per the departmental protocol.

Weight and BMI of the patients were measured and calculated postpartum.

Primary Outcomes

Rates of recurrence of convulsions, magnesium sulfate toxicity, and maternal mortality.

Secondary Outcomes

Rates of organ failure (morbidity-liver failure, renal failure, HELLP syndrome, disseminated intravascular coagulation, stroke and pulmonary edema), mode of delivery, stillbirth, perinatal death, and neonatal death.

Statistical analysis was done to compare efficacy and safety of above two regimes used in our institute by analyzing variables like recurrent convulsion rate and rate of toxicity due to magnesium sulfate therapy using Chi-square test and Fisher's exact test where appropriate (*p* value < 0.05 was considered as significant).

RESULTS

Group I—consisted of 189 cases and group II had 52 cases. Table 1 shows where there was the matching of age and gravidity distribution, socioeconomic status, referral status, residence, availing antenatal care, type of admission, types of eclampsia, the severity of blood pressure and proteinuria. The only difference was BMI, in group I could not be calculated because of retrospective data in group II 17.3% patients were underweight and 82.7% had normal weight. Table 2 indicates magnesium sulfate therapy received by group I and group II. A major difference between the two groups was maintenance dose in group I 1 g/hour and group II 0.5 g/hour. The mean magnesium level was around 3.3 mEq/L in group II which was not done in group I (not possible due to the retrospective nature of the data). The total dose received in 24 hours in group I was 28 g and in group II which was 16 g. So in group II total dose received was 12 g less than group I. Recurrent convulsion rate was 5% in group I and 9.6% in group II which was statistically not significant (*p* value 0.312 by Chi-square test). Toxicity was seen in 15.3% cases in group I while it was not seen in group II and difference was statistically significant (*p* value 0.001 by Fisher's exact test). Table 2 shows the

Table 1: Demography and clinical profile of study groups

	Zuspan regime (group I) (n = 189)	Low maintenance dose regime (group II) (n = 52)
<i>Epidemiology data</i>		
Age distribution	23.6 ± 4.17	23.3 ± 4.16
<i>Parity distribution</i>		
Primi (g1)	68%	63.4%
Multigravida (g2–g3)	29%	32.6%
Grandmulti (g4)	3%	5.7%
<i>Residence</i>		
Rural	80%	78.2%
Urban	20%	21.8%
<i>Socioeconomic class</i>		
Lower	80%	77%
Referred cases	82%	78.2%
<i>BMI (kg/m²)</i>		
Under weight (<18.5)	Na	17.3%
Normal weight (18.5–24.99)	Na	82.7%
<i>Antenatal care</i>		
Taken	9%	21%
Not taken	91%	73%
<i>Type of admission</i>		
Emergency	99%	98.1%
Booked	1%	1.9%
<i>Clinical profile</i>		
<i>Type of eclampsia</i>		
Antepartum	65.6%	59.6%
Intrapartum	19.5%	19.2%
Postpartum	12.1%	21.1%
<i>Symptoms</i>		
Pedal edema	58%	57.6%
Headache	50%	53.8%
Vomiting	23%	23%
Blurring of vision	29%	19.2%
Epigastric pain	3%	11.5%
Oliguria	5%	9.6%
<i>Blood pressure</i>		
Severe	72.2%	48%
Mild	16.4%	32.6%
Normal	9.5%	19.2%
<i>Proteinuria</i>		
≤+2	52%	36.6%
>+2	48%	63.4%

mode of delivery and maternal and fetal outcome. It is significant to note that the maternal mortality rate in group I was 1.5% whereas there was no mortality in group II. Although perinatal mortality rate 44/1,000 live births in group I and 26/1000 live births in group II. Table 3 is a compilation of different magnesium sulfate regime with reference to recurrence convulsion rate and maternal mortality. In our study, we had zero mortality.

DISCUSSION

The present study was carried out to compare the effects of the standard-dose regime used for Eclampsia (Zuspan) and another low dose (IV) regime with a 50% reduction in maintenance dose.

Table 2: Comparison of MgSO₄ low dose vs zuspan regime

	Zuspan regime (group I) (n = 189)	Low maintenance dose regime (group II) (n = 52)
<i>Magnesium sulfate therapy</i>		
Loading dose received outside (extramural)	15.8%	23%
Loading dose received inside (intramural)	85%	67%
Maintenance dose	1 g/hour	0.5 g/hour
<i>Serum mg level</i>		
		Safe range – 2.5–7.5 mEq/L
		Therapeutic range 2.5–5 mEq/L
1st sample	na	3.4 (mean)
2nd sample	na	3.32 (mean)
3rd sample	na	3.3 (mean)
Total magnesium sulfate dose in 1st 24 hours	28 g	16 g
Effectiveness of magnesium therapy	95%	90.4%
Recurrent convulsion rate*	5%	9.6%
Toxicity rate**	15.3%	0
<i>Maternal and fetal outcome</i>		
<i>Mode of delivery</i>		
Vaginal	72.5%	65.3%
Instrumental vaginal	2.1%	5.7%
Cesarian section	25.3%	28.8%
Maternal mortality	1.5%	0
Perinatal mortality rate***	44/1000 live birth	26/1000 live birth

*p value 0.312 statistically not significant difference by Chi-square test

**p value 0.001 statistically significant difference by Fisher's exact test

***p value 0.039 statistically significant difference by Chi-square test

The phase-II of the present study was specifically designed to suit rural women of Gujarat who is weighing around 50 kg (BMI-25) or less. Our aim was to minimize magnesium sulfate toxicity while maintaining its anticonvulsant effect. Recurrent convulsion rate while using a low maintenance dose regime in the present study was 9.6%. Which was comparable to other studies like Joshi's VIMS regime (9.16%)¹⁴ and Suman Sardesai's low dose magnesium sulfate regime 11 (7.8%).¹⁵ Recurrent convulsions after therapy (if at all occurred) could be controlled immediately by giving 2 g (20% solution) IV as a loading dose followed by 1 g/hour IV maintenance dose without any serious consequences. There were no maternal complications due to recurrent convulsions because patients were under close monitoring and immediately the stepping up of the dose was enough to control the convulsions. Different clinical signs of toxicity of magnesium sulfate were not encountered in the low dose MgSO₄ group in the present study. None of the patients required discontinuation of magnesium sulfate therapy before time decided in the protocol. We could achieve a serum magnesium level around 3.3–3.4 mEq/L with low maintenance dose magnesium sulfate therapy. These serum magnesium levels of patients were below therapeutic range for eclampsia but within the range of normal blood level. An important observation was that

Table 3: Comparison of recurrent convulsion rate and maternal mortality with different regimes of magnesium sulfate therapy

S. no.	Studies	Loading dose IM/IV	IM/IV maintenance dose	Total MgSO ₄ dose (g) in first 24 hours	Recurrent convulsion (%)	Maternal mortality (%)
1	Pritchard et al. ⁹	4 g IV plus 5 + 5 g IM	5g/4 hourly IM	39	2.85	2.1
2	Zuspan et al. ¹⁰	4 g IV	1 g/hour IV	28	23.8	
3	Begum et al. (Dhaka regime) ¹⁶	4 g IV plus 3 + 3 g IM	2.5 g/4 hourly IM	22.5	1.53	8.6
4	Jana et al. (Jana regime) ²⁷	3 g IV plus 2.5 + 2.5 g IM	2.5 g/4 hourly IM	20.5	6.1	2.7
5	Suman Sardesai et al. ¹⁵	4 g IV IM or IV	2 g/3 hourly	20	7.8	2.6
6	Joshi et al., (VIMS regime) ¹⁴	4 g IV + 4 g IM	–	8	9.16	3.3
7	Chowdhury et al., (low dose maintenance) ²⁸	4 g IV	0.6 g/hour IV	18.4	2	3.3–5
8	Ekele et al. (ultra short regimen) ²⁹	4 g IV plus 5 + 5 g IM	–	14	7.4	9.9
9	Low maintenance dose in present study (phase II)	4 g IV	0.5 g/hour IV	16	9.6	0

convulsions were under control in our patients with a subtherapeutic range of serum magnesium which was also observed by Dhaka regime.¹⁶ A pharmacokinetic study done by Dayicioglu et al. concluded that increasing BMI is inversely proportionate to serum magnesium level, while eclamptic convulsions did not correlate with either body mass index or circulating plasma magnesium levels.¹⁷

So routine measurement of magnesium level is not recommended. It may be checked when there is a sign of magnesium sulfate toxicity. MgSO₄ total dose requirement in the study group goes down by almost 43% in our study compared to Bhattacharjee et al.¹²

As far as toxicity of magnesium sulfate therapy was concerned, there was a remarkable difference that was also statistically significant. Maternal mortality was also nil, and the perinatal mortality rate was decreased in group II of our study. We intend to continue the low maintenance dose regime study in our hospital to increase the strength of our experience.

Strengths and Limitations

The present study is only of its kind that shows the safety and importance of intravenous regime which gives a uniform level of magnesium without significant fluctuation. Use of intramuscular regime for treatment of eclampsia leads to temporary high levels of magnesium sulfate and more fluctuations in its serum levels which can be a cause for magnesium toxicity.^{18,19}

Toxicity of magnesium sulfate in the form of depression of deep tendon jerks, respiratory or cardiovascular effects was not encountered in the present study which was a very strong benefit of dose reduction. It can be recommended for women of average weight (≤ 50 kg and BMI ≤ 25) India, Bangladesh, Nepal, Japan, etc., while taking care of decreasing or eliminating iatrogenic overdose.^{20–25}

Limitation of the present study was less number of patients. The study was not a randomized comparison with similar weight control was not possible in our study.

Future research needs more multicentre case-control studies to support the observation in women with similar weight controls.

Interpretation

It was found that low maintenance dose regime was effective in our study although we need to have a number of studies that may be randomized control trials and multicentric trials in Gujarat and India to establish the ideal dose of magnesium sulfate for smaller women (around ≤ 50 kg).

Generalization of Outcome and Recommendations

The method of delivering low maintenance dose of magnesium sulfate intravenously is relatively controlled, easy and healthcare workers can be trained for the same at all FRU (first referral units). It requires syringe pumps or infusion pumps for safe and controlled administration of magnesium sulfate. They are most probably available in secondary care centers of government setup (CHC). The IV administration of magnesium sulfate has an advantage over intramuscular injection as it reduces the chances of injection abscess and agony of pain which is very common with magnesium sulfate due to its high concentration (50%), IV ensures uniform distribution of the drug in the body. This reduces the long-term morbidity of the patient, hospital stay and treatment cost. Timely administration of MgSO₄ in low dose will empower treating doctors at the periphery without fear of toxicity to reduce maternal morbidity and improve overall maternal and fetal outcomes.

CONCLUSION

We concluded that in patients weighing less than or equal to 50 kg, a low maintenance dose of magnesium sulfate is as effective as the standard regimen (Zuspan) for controlling convulsions and may be superior in decreasing toxicity.

We recommend intravenous low maintenance dose can be used in secondary care centers—CHCs. It improves maternal and fetal outcomes. It also reduces the chances of toxicity of magnesium sulfate, although it requires proper infrastructural facilities (syringe pump), education and training of doctors and nursing staff and good monitoring of patients. Application of low dose IV maintenance regime on a larger scale in government setup can improve survival of many eclampsia patients.

CONTRIBUTION TO AUTHORSHIP

The study arouses from an original idea from Smruti B Vaishnav, Nitin Raithatha, Krina Kathawadia contributed to study design. Rakhee Patel contributed to the study of retrospective data. All authors contributed to the discussion and conclusion.

ETHICS APPROVAL

This study was approved by the Human Research Ethics Committee, HM Patel Centre For Medical Education and Research, Karamsad.

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