Original Article

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'Single Dose MgSo4 Regimen' for Eclampsia - A Safe Motherhood Initiative

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ABSTRACT

Objectives: To determine the efficacy and the safety of the single dose MgSo4 ('VIMS') regimen in treating eclamptic seizures and their effect on the maternal and foetal outcomes.

Methods: A prospective, observational study was conducted in the period from 2003 to 2007. 513 eclamptic women who were admitted to the Dept of OBG, VIMS, Bellary, received single doses of 4g diluted 50% Mgso4 intravenously, with simultaneous 4g 50% MgSo4 intramuscularly. The recurrent seizures, maternal mortality and the perinatal mortality were measured.

Results: 9.16% of recurrence (11.66%-16.49%), 3.3% of maternal mortality (1.8%-4.9%) and 24.8 % (21.1%-28.7%) of perinatal mortality were observed. The statistical analysis was done by using confidence intervals, standard deviations, means and the Standard normal "Z" test.

Conclusion: The single dose MgSo4 regimen is effective and safe in controlling eclamptic convulsions. The 'VIMS' regimen can be used at First Referral Units, before shifting the patients to tertiary care centres. This approach has special implications in the developing countries, especially at the primary care level, where the standard obstetric care is not widely available.

Key Words: Eclampsia, Single dose MgSo4, Maternal mortality

INTRODUCTION

Eclampsia is one of the important direct causes of maternal mortality. The eclampsia related mortality can be reduced by an early referral and an effective institution of anticonvulsant therapy. MgSo4 is the anticonvulsant of choice for eclampsia. The postulated mechanism of MgSo4 includes central and peripheral actions. In the central action, the blockade of NMDA (N methyl D aspartate), a subtype of the glutamate channel receptor with a potent cerebral vasodilatation, is demonstrated by Doppler studies. Peripherally, at the neuromuscular junction, MgSo4 causes the blockage of calcium, which enters the cell and blocks the calcium at the intra cellular sites, with a resultant reduced neuro muscular irritability. The direct action of a neuro muscular block, though it has been suggested, seems unlikely, as the serum concentration for its anti convulsive action is well below that which is needed for a neuro muscular block. In the past decade, researchers from the developing countries were constantly striving to steadily decrease the dosages of both the loading and the maintenance doses of the MgSo4 regimens to suit the local conditions. There is a delay in starting the MgSo4 therapy at peripheral centres. Most often, eclamptic women are referred to tertiary care hospitals in a moribund state without giving a proper anticonvulsant therapy, with consequent, poor, foeto-maternal outcomes. Such a catastrophe can be avoided if the MgSo4 therapy is started outside the obstetric centers at the earliest. Steadily, there has been a change in the use of the MgSo4 regimen in our institution, starting from the standard Pritchard regimen [1] to the low dose MgSo4 regimen, as has been described by Suman Sardesai [2]. A pilot study (2000-2002) comparing Pritchard regimen, low dose MgSo4 and single dose MgSo4, was done in our institution. The efficacy and safety of a single dose was comparable to those of other regimens. After realizing that the loading dose itself could abolish the seizures in more than 90% of the cases and after being reassured about the safety of MgSo4 from various studies, we propose that single dose MgSo4 can be given at the peripheral centre (first referral unit-FRU) by trained health personnel. It would result in a near seizure free transport to the higher centers where a disciplined and definitive treatment can be readily instituted.

MATERIALS AND METHODS

A total number of 513 cases of eclampsia were treated with single dose MgSo4.The study period was from 2003 to 2007. Women with a provisional diagnosis of antepartum, intrapartum and postpartum eclampsia, who were admitted to the Labour and Delivery Unit of the Dept of OBG, VIMS, received the single dose protocol. Women with epilepsy and convulsions 5 days post partum, were excluded from the study.

Protocol: A loading dose of 4gm of 50% MgSo4 was given intravenously after diluting it in 20cc of 5% Dextrose over 10-15min and simultaneously, 4gm of undiluted 50% MgSo4 was administered intramuscularly. If convulsions occurred within 30 minutes of starting the therapy, no additional MgSo4 was given. If the convulsions were not controlled even 30 minutes after giving the single dose MgSo4, it was considered as a recurrence. These patients were switched over to other regimens like Sardesai's low dose MgSo42 regimen i.e. 4g of Mgso4 was given as a loading dose and thereafter, 2g of MgSo4 (intramuscularly or diluted intravenously) was given as a maintenance dose every 3rd hourly. Alternatively, the standard Pritchard regimen [1] which consisted of 5g of MgSo4 was given every 4th hourly, depending on the eligibility criteria, which was based on the clinical assessment of the deep tendon reflexes, the respiratory rate and the urine out

put. Or the Phenytoin regimen [3] which consisted of 10mg/kg MgSo4 was given intravenously at 0 hours, followed by 5mg/kg iv at 2 hours and 500 mg iv at 14 hours. 200mg/8h for 5 days was given as maintenance. As the loading dose of MgSo4 was already given, only the maintenance dose of low dose MgSo4 [2] or Pritchard [1] was used in recurrence cases. A switchover 2nd line treatment was given on the choice of the consultant in charge.

The patients were monitored for Magnesium toxicity and 10% calcium gluconate was kept ready to treat any toxicity which could occur. As the facilities for an invasive haemodynamic monitoring were not available in our hospital, oral nifedepine was used as an anti hypertensive agent. 10mg of nifedepine was used 8th hourly. If the blood pressure was >160/110 mm of Hg, an additional dose of 10mg was used every 30-45 minutes, up to a maximum dose of 80 mg/day. The fluid replacement therapy which was given was the Ringer Lactate solution or normal saline. The underlying diseases/associated complications were also noted. An input output monitoring was done and termination of the pregnancies was planned. If the patients were already in labour, ARM and augmentation of the labour were done. PGE2 gel priming of the cervix was used in certain cases. LSCS was done for standard obstetric indications. In these women, the liver function test, renal function test, platelet count and other routine biochemical investigations were carried out.

RESULTS

During the 5 year study period (2003 to 2007), there were 513 cases of eclampsia among 19,620 deliveries (1 in 26 deliveries), which gave an incidence of 2.6%. Out of the 513 women, 71.5% were in the age group of 20-30 yrs. Only 1.6% women were more than 30 years of age. 75% of the women were primi gravidae. The mean age was 21.5 years, with a standard deviation of 3.4.The mean gestational age was 33.04 weeks, with a standard deviation of 1.34. In 41.14% % of the cases, the gestational age was less than 34 weeks of gestation. 28.1% of the cases were unbooked cases [Table/Fig-1].

Basic characteristics	Number	%	95% CI
Age in years (n=513)			
<20	138	26.9	23.8-30.1
20-30	367	71.5	68.2-74.8
>30	8	1.6	0.6-2.4
Parity (n=513)			
Primigravidae	385	75.0	71.9-78.1
Multigravidae	128	25.0	21.8-28.1
Registration (n=513)			
Booked	369	71.9	68.6-75.1
Unbooked	144	28.1	24.1-31.3
Gestational age (wks) (n-513)			
<28	43	8.31	
28-34	168	32.74	Mean-33.04wks
34-37	116	22.60	SD- 1.34
>37	186	36.24	

[Table/Fig-1]: Basic characteristics of subjects studied

89.7% of the women had ante partum and intrapartum eclampsia. As the precise diagnosis of the onset of labour was not easily ascertainable and as eclampsia per se increases the uterine contractility and leads to premature labour, a discrete overlap between the ante partum and the intrapartum cases may exist. Postpartum eclampsia accounted for 10.3% of the cases. 62.2% of them had less than 4 episodes of convulsions before the single dose MgSo4 treatment was given. The number of convulsions prior to the single dose did not affect the recurrence, because among 47 women who had recurrence of convulsions after the 'VIMS' regimen, only 3 cases had >10 episodes of convulsions at admission. 87.5 % of the patients did not receive any treatment before admission. Most of the women were referred from rural peripheral centres and many of these women were not booked in our institution.The convulsion to treatment interval was more than 6hrs in 30.2% of the cases. The Mean Arterial Pressure (MAP) was >110 mm of Hg in 82% of the cases. The mean of MAP was 124.2 mm of Hg, with a standard deviation (SD) of 16.38. 65% of the recurrent cases had a mean arterial pressure >110 mm of Hg. This showed that an adequate control of the blood pressure is also an important step in the management of eclampsia.

Primary outcome	Number	%	C.I
Recurrence (n=513)			
Controlled	466	90.84	88.3-93.3
Uncontrolled	47	9.16	6.6-11.6
2nd line treatment (n=47)			
Low dose MgSo4	33	70.2	57.1-83.2
Pritchard's	10	21.2	9.5-32.9
Phenytoin	4	8.5	0.5-16.4
Maternal mortality	17 (17/513)	3.3	2-4.6
In recurrent cases	2 (2/47)	4.2	0-10
In non-recurrent cases	15 (15/466)	3.2	1.6-4.8
Perinatal mortality (n=497))	124	24.9	21.1-28.7
IUD	66	13.2	
Still born	45	9.0	
Early neonatal death	13	2.6	

[Table/Fig-2]: Primary outcome measures

The convulsions were controlled in 90.84% of women (CI 88.3-93.3) i.e., recurrence of the convulsions occurred in 9.16% (CI 6.6-11.6) of the women after they received the single dose regimen. 35% of the cases had recurrence, even after switching over to the 2nd line of treatment. None of the women who were treated with the single dose VIMS regimen required calcium gluconate to counter the toxicity. No side effects were seen with this regimen. Overall, the maternal mortality was 3.3% (17 out of 513) in our study (CI 2-4.6), [Table/Fig-2]. 3.2 % of the mortality was seen in the non recurrent cases and 4.2% mortality was observed in the recurrent cases. Intracranial haemorrhage (10 out of 17 deaths) was the leading cause of death, which accounted for 58.8% of the fatal cases. All these women were admitted in a moribund state. 2 cases of recurrence died of intracranial haemorrhage after they received the single dose regimen. Pulmonary oedema (5 out of 17 deaths) was the second leading cause of death (29.4%) [4] (2.1%) women had the HELLP syndrome. However, only 1 woman had recurrence after taking a single dose of MgSo4. Abruptio placentae was seen in 10(1.94%) cases with no recurrence of convulsions in these women. 23 women (4.5%) had severe anaemia with 2 cases of recurrent convulsions. 3(0.6%) women had cortical blindness and 4(0.77%) women suffered acute renal failure

with no recurrence of the convulsions. The single dose MgSo4 therapy was independently associated with the control of the convulsions, despite the adverse pregnancy outcomes.

The delivery data was available only for 497 women, as 11 women died undelivered and 5 women left the hospital against advice after receiving the treatment. 443 women (89.1%) had vaginal deliveries and caesarean sections were performed in 54(10.9%) cases. 90% of them were done for foetal indications. The mean birth weight was 1.95 kg, with a SD of 0.41. The perinatal mortality was 24.9%. The relatively high PMR rate was due to prematurity, low birth weight and 66 (13.2%) cases of IUD [Table/Fig-2].

DISCUSSION

The collaborative group concluded, "there is now compelling evidence in favour of Mgso4 for the treatment of eclampsia" [5]. Since the introduction of the Pritchard regimen [1], there has been a constant discussion in the literature regarding the dose of Magnesium sulphate.

As was discussed in the Magpie trial report of 2002, the most important question would be, 'what is the minimal effective dose? [6]. "If a women is known to be/appears to be small, the dose should probably be limited [1]. In recent years, Andrea Witlin, in her review article on eclampsia, commented, "One may also speculate that the Magnesium sulphate dosing should vary according to the patients' weights or body mass indices. However, this has never adequately been evaluated" [7].

In our study, the efficacy of the single dose regimen was comparable to those of other studies [Table/Fig-3]. Pritchard [1] reported recurrence in 12% of the cases. The collaborative eclampsia trial group reported a recurrence of 5.3%-13.2% [5]. Most of the studies [2, 8-10] which were done in the Indian subcontinent, have modified the original Pritchard regimen to suit the local conditions. Mostly, these regimens involved a steady decrease in both the loading as well as the maintenance doses, with acceptable success rates [Table/Fig-3].

Regimen	Recurrence	Maternal mortality	Author
Single Dose MgSo4	9.16%	3.3%	Joshi&Veerendrakumar
Pritchard	12%	0.4%	Prichard et al., [1]
Low Dose MgSo4	7.8%	2.6%	SumanSardesai et al., [2]
Eclampsia trial group	5.3–13.2 %	3.8-5.2%	Eclampsia trial group [5]
Dhaka regimen	1.53%	8.6%	Begum et al., [8]
Padhar regimen	1.05%	-	Mahajan [9]
Low dose maintenance	2%	3.3-5%	Chowdhury [10]

[Table/Fig-3]: Comparison of various MgSo4 regimens

The results of the Magpie Trial [6] suggest that a shorter course of the treatment may be adequate. In this study, most of the women probably received only the loading dose injection before being referred to the recruiting hospital. For these women, there was no difference in the outcome between those who were given further magnesium sulphate or placebo (relative risk 1.24, 95% CI 0.49—3.11). The argument for a short course was further supported by the trial data, which suggested that the drug could continue to be beneficial long after the treatment was given. Since eclamptic fits can occur at any time up to 7 days after the delivery, for most of the time at which the women were at risk, they would have had sub therapeutic serum concentrations of magnesium sulphate. Despite this situation, the prophylaxis seems to have been successful [6]. To make magnesium sulphate available to the women who are at a risk of eclampsia, a short regimen is suitable for use in the underdeveloped countries–ideally, this would include a single magnesium sulphate injection [11].

In our institution, there has been a steady shift in the anticonvulsant regimen which was used in the last decade. Till the late 90s, the Pritchard regimen was used; subsequently (1998-2002), low dose MgSo4 [2] was used and from 2003 onwards, the single dose MgSo4 regimen is being used, with a good success rate. In our institution, a pilot study was undertaken to know the efficacy and the safety of single dose MgSo4 in the treatment of eclampsia. In a study which was done on 224 eclampsia cases during 2000-2002, 94 women received single dose MgSo4 as has been mentioned in the 'materials and methods' section,102 women received low dose MgSo4 as was described by Sardesai [2] and 28 women received the standard Pritchard regimen [1]. The recurrence rate was 12.7% (12/94) in the single dose group, 12% in the low dose group and 3.5% in the Pritchard group. The maternal mortality was 1% in the single dose group; no maternal deaths were noted in the low dose group and in the Pritchard group, 14% women died of intracranial haemorrhage. Gaddi and Somegowda [4], who were from the same institution, reported the data on 791 cases (from 1998-2004). Among these, 621 received the low dose MgSo4 regimen [2], 90 women received the single dose as has been described earlier and 72 cases were treated with the standard regimen of Pritchard [1]. The recurrence rate of the convulsions was 9.2% in these cases [Table/Fig-4]. The maternal mortality is 3.3% in this study; Gaddi [4], from the same institution, reported 5.4% mortality. The historical data of the various outcomes have been compared in [Table/Fig-4], as the study was done in similar settings. The standard "Z" test was done and the statistical analysis showed that the single dose was better than the MgSo4 regimen which was used in Gaddi's [4] study in terms of a reduced maternal mortality, perinatal mortality and associated complications [Table/Fig-5].

Outcome	Joshi et al., 2003-2007	Gaddi et al., 1998-2004
Recurrence	9.16%(47/523)	9.2(73/791)
Maternal mortality	3.3% (17/513)	5.4%(43/791)
Perinatal mortalty	24.8%(124/497)	39.3%(302/768)
Severe complications	11.7%(60/513)	16.3%(129/791)
HELLP syndrome	11 (2.1%)	1(0.2%)
Abruption	10(1.94%)	24(3%)
Pulmonary edema	8(1.56%)	28(3.5%)
Aspiration pneumonia	7(1.3%)	21(2.7%)
Post partum hemorrhage	6(1.16%)	14(1.8%)
Cortical blindness	3(0.6%)	14(1.8%)
Acute renal failure	4(0.77%)	9(1.1%)
Intracerebral hemorrhage	10(1.94%)	18(2.2%)

[Table/Fig-4]: Historical comparison of outcome in the same institution

	Joshi et al., (Current study)			Gaddi et al.,			Significant if Z > 1.645	
Outcome	N1	X1	P1	N2	X2	P2	SD	Z
Recurrence	513	47	9.16	791	73	9.2	1.64	0.04
Maternal mortality	513	17	3.3	791	43	5.4	1.13	1.88
Perinatal mortality	497	124	24.9	768	302	39.3	2.62	5.48
Complications	513	60	11.7	791	129	16.3	1.93	2.39

[Table/Fig-5]: Single tailed Z test comparing historical data using different Regimens in the same institution

In the collaborative eclampsia trial (CET) Group [4], the mortality was in the range of 3.8% - 5.2%. Chowdhury et al., [10] reported 3.3-5% maternal mortality and Sardesai [2] reported 2.6% maternal mortality. Begum et al., [8], in their study in the period from 1998 to 2000, reported that the rate of maternal deaths from eclampsia was 8.6%, which was lower than that of the immediate past year (1997), for which the mortality was 16%. Changing the protocol from diazepam to magnesium sulfate for the control of convulsions significantly reduced the incidence of death. But the reduction of the risk of death was difficult when the patients developed complications. Most of the patients in the group who had complications, died (98%); these complications developed as a result of a delayed decision for the treatment. Therefore, efforts should be directed to develop awareness to receive the treatment at an appropriate time, to prevent the development of eclampsia and to reduce the mortality which occurs due to eclampsia and its complications [8]. The mortality rate is relatively more in the resource poor settings of the developing countries. In the Sibai study [12] the excellent maternal outcome was attributed to the experience of the physicians and the use of a standardized protocol. In contrast, Lopez-Llera reported 13.9% maternal deaths while Adetoro reported a 14.4% maternal mortality. However, many of these patients were admitted in a moribund state, with multiple complications. This finding emphasizes the importance of an early and a proper referral of such patients [12]. The anticonvulsant regimen alone cannot change the maternal and foetal outcomes. 3.2% (15/466, CI 1.6-4.8) of the patients had mortality despite the non recurrence of seizures [Table/Fig-2]. The other principles of the eclampsia management should be simultaneously and effectively instituted. Sibai recommends that the patients should be stabilized with respect to their blood pressures and the control of convulsions before they are transported and that the patients should be sent in an ambulance with medical personnel in attendance [12]. In tertiary care centres, the other causes of maternal mortality like hypertensive crises, the left ventricular diastolic dysfunction, ARF, coagulatory disorders etc, can be closely monitored and treated to reduce the maternal mortality and morbidity.

Despite the compelling evidence which is there in favour of MgSo4, the health personnel at the primary care level do not administer MgSo4. Most of the eclamptic women either receive no immediate treatment or they receive some anticonvulsants like diazepam and they are then sent to tertiary care centres for further management. The transportation of these highly irritable eclamptic women is far from ideal, in most of the third world countries, including India. In this study, 87.5% of the patients did not receive any treatment before their admissions. Most of the women were referred from peripheral centres. Precious time was wasted during their transit. Instead, they could have received this treatment at the peripheral centre itself. The need of the hour is to arrest seizures at the earliest, especially in Primary Health Care (PHC) settings, so that the convulsion to treatment interval is brought to minimum. This strategy will help in improving the maternal and foetal outcomes.10% of these patients may convulse again after receiving the loading dose. This recurrence may be acceptable, considering the potential benefits of the seizure control during their transportation to the higher centers. According to Sibai [13], most of the eclamptic women will become seizure free after they are given an additional dose of 2g MgSo4. The administration and the clinical monitoring of magnesium sulphate can be done by medical, midwifery, or nursing staff, provided they are appropriately trained. This achievement has obvious implications for care, particularly in the low-income and the middle-income countries [5].

CONCLUSION

The very fact that there is no single standardized protocol in the world, gives scope for tailoring the MgSo4 regimen according to the local needs. This becomes all the more relevant in resource poor settings. The single dose MgSo4 VIMS regimen is simple and efficient. The single dose regimen can be safely used outside the established obstetric centres (at the primary health care level itself, where maximum number of cases of eclampsia occur) and the cases can be transferred to tertiary care centres for a definitive and a disciplined management of these cases. Thus, crucial time is not wasted and an almost seizure free transportation can be ensured. The convulsion to medication interval is brought to minimum.

As was envisaged by the Magpie trial [5], Andrew d weeks [10] and based on the encouraging results of our studies, we propose that the shorter MgSo4 therapy should be readily available for immediate use at the primary care levels. The doctors and the trained paramedical staff should be extensively made aware about the single dose of the MgSo4 therapy. As a part of the safe motherhood initiative, we sincerely hope and wish that this 'VIMS' regimen will become the standard protocol at primary care levels and answer the problem of an early treatment and referral, even at the hands of non obstetrician physicians. Thus, many more lives of mothers can be saved.

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