Loading Dose only versus Standard Dose Magnesium Sulfate Seizure Prophylaxis in Severe Pre-eclamptic Women

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ABSTRACT

Introduction: Magnesium sulfate is the drug of choice for prevention of seizures in the pre-eclamptic woman. There is no agreement in the published randomized trials regarding the optimal time to initiate magnesium sulfate, the dose to use (both loading and maintenance) as well as the duration of therapy. The objective of this study is to determine whether magnesium sulfate prophylaxis is needed for up to 24 hours postpartum in all patients with severe pre-eclampsia for the prevention of seizure.

Methods: It is a randomized controlled trial conducted on 60 pregnant women with severe preeclampsia randomized into standard dose and loading dose only regimen.

Results: Out of 30 cases in each group 1 (3.3%) patient in standard regimen and 2 (6.7%) patients in loading dose only developed seizure. The occurrence of seizure is not significant statistically. In both regimens, there was no maternal mortality. Total of 3 patients needed MICU care and 12 patient developed maternal complications. MgSO4 toxicities were seen only in standard dose regimen that is in 17 (56.7%) of the patients. The median number of IM injections of MgSO4 received in standard dose regimen was 8±2.176. In standard dose regimen 73.3 percent baby were alive whereas in case of loading dose only regimen 93.3 percent of baby were alive after 48 hours of delivery.

Conclusions: Single dose of magnesium sulfate is equally effective as standard dose regimen in terms of seizure prophylaxis in severe pre eclamptic women, with added advantage of reduced maternal toxicity and better neonatal outcome.

Keywords: *severe preeclampsia; MgSO4; magnesium sulfate; loading dose; eclampsia.*

INTRODUCTION

Hypertensive disorders of pregnancy affect about 10% of all pregnant women around the world.[1,2] The preeclampsia affects 2-8% of all pregnancies worldwide.[2] The primary aim of treatment in severe preeclampsia is to prevent eclamptic seizures, and resultant morbidity and mortality. Magnesium sulfate (MgSO4) is the drug of choice for prevention of seizures in the pre eclamptic woman, or prevention of recurrence of seizures in the eclamptic woman.[3,4]

There is no agreement in the published randomized trials regarding the optimal time to initiate magnesium sulfate, the dose to use (both loading and maintenance), the route of administration (Intramuscular or intravenous), as well as the duration of therapy.[5] The resultant limited duration of magnesium exposure, cost savings, and decreased patient discomfort and inconvenience make this an attractive option for patients and clinicians.[6]

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The main objective of the present study is to see whether all severe pre eclamptic women need magnesium sulfate (MgSO4) as seizure prophylaxis for 24 hours.

METHODS

A randomised control trial was carried out in the Obstetrics unit of department of Obstetrics and Gynecology, BPKIHS, Dharan in 12 months duration from August 2014-July 2015. The study was started after approval by Institutional Ethical Review Board (IERB) of BPKIHS. The Study population was diagnosed cases of severe preeclampsia, who were admitted to the ward, gave written informed consent for participation in the study and were in labour or planned for termination of pregnancy. Patients with period of gestation less than 20 weeks and who have received magnesium sulfate before admission to the ward were excluded from the study.

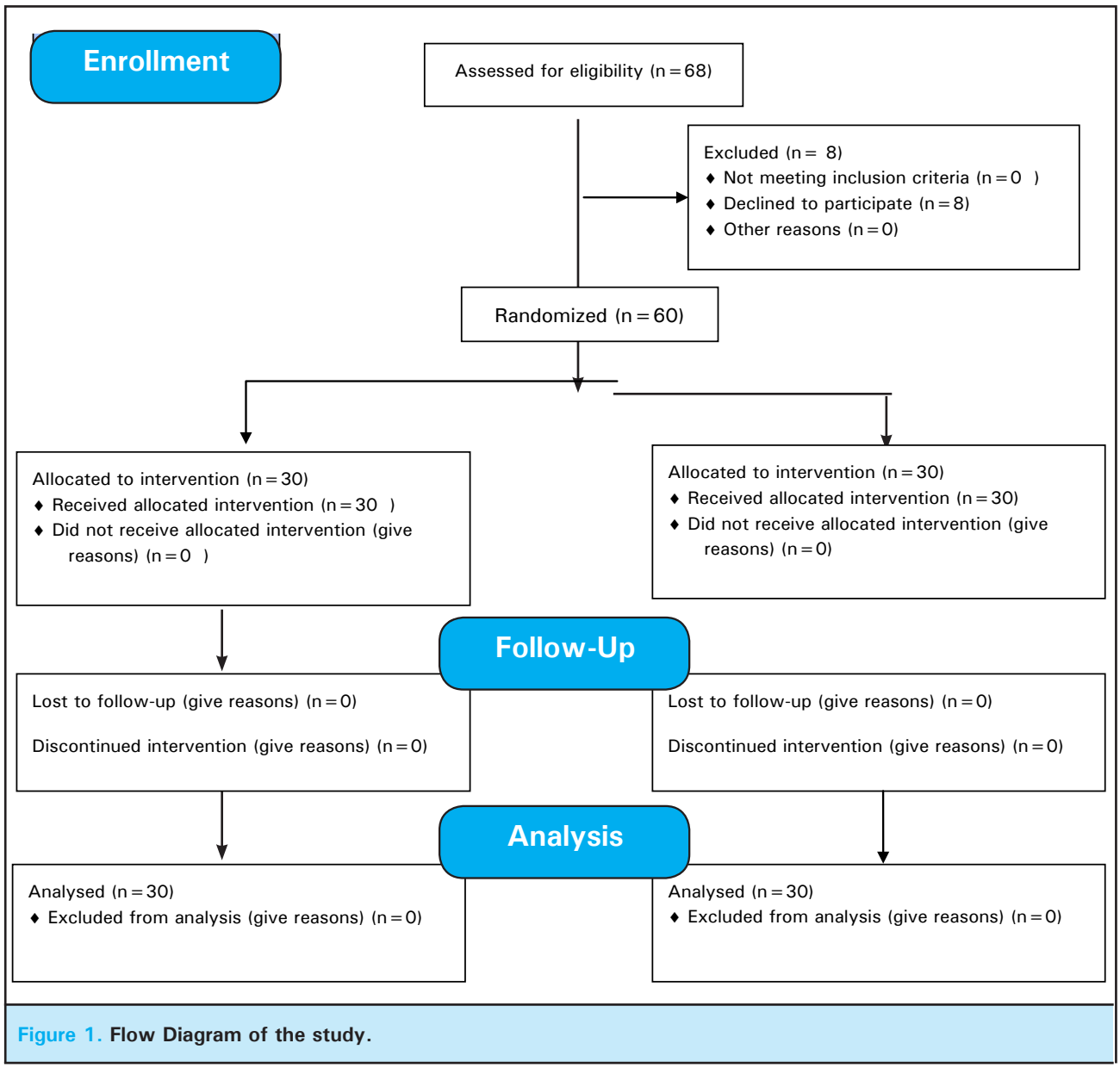

Figure 1. Flow Diagram of the study.

The participants were randomized to either Group A (Standard Dose, Pritchard Regimen receiving group) or the Group B (Loading Dose only receiving group) after informed consent was obtained. The Group A received standard dose. The standard dose means loading dose as well as maintenance dose. Maintenance dose means injections of MgSO4, IM every 4 hours for 24 hours from the time of delivery or the last seizure which so ever is longer. The Group B received only loading dose and other injections of MgSO4 discontinued after the first dose.

Loading dose was given as 4 gm of 20% magnesium sulfate IV over 5 minutes plus 5 gm of 50% magnesium

sulfate on each buttock hence total of 14 gm magnesium sulfate. Intravenous fluids were discontinued unless indicated owing to surgery. These women were closely monitored as per the institute protocol that is up to 24 hours of delivery. Blood pressure, urine outputs were measured and sign symptoms of impending eclampsia were assessed. Monitoring of MgSO4 toxicity was continued in the form of checking patellar reflex, urine output measurement, and respiratory rate. For the recurrence of seizure in any of the above group injection of magnesium sulfate 2gm, IV, 20% was given over 5 minutes. Once MgSO4 was reinstituted, it was continued until the completion of 24 hours after delivery or the last dose whatsoever is longer. Anti-hypertensive drugs were started or discontinued for both groups, as per the existing protocol of the institute.

Total of 60 (30 in each arm) patients with severe pre-eclampsia were enrolled in the study. The sample was calculated by the formula given below

$$n = \frac{(z_\alpha \sqrt{\bar{p}\bar{q}} + z_\beta \sqrt{p_1 q_1 + p_2 q_2})^2}{(p_1 - p_2)^2}$$

Where $\bar{p} = \frac{p_1 + p_2}{2}$ and $\bar{q} = \frac{q_1 + q_2}{2}$

$z\alpha = 1.96$ at 95 Confidence interval and $z\beta = 0.842$ at P = 80%

$p_1 = 8\%$ and $q_1 = 1\text{-}p_1 = 92\%$

$p_2 = 20\%$ and $q_2 = 1\text{-}p_2 = 80\%$

Based on the literature percent of getting seizure in a severe preeclamptic women who receives 24 hrs Magnesium sulfate prophylaxis is 8% and assuming the percentage of getting seizure to the patient getting single dose magnesium sulfate be 20%.[1]

Keeping these values at above formula sample size comes to be 133 and taking 20% more it comes out to be around 150.

Again, from WHO CDC Atlanta Finite sample size calculation is

$$n = \frac{\text{calculated sample size}}{1 + \frac{\text{calculated sample size}}{\text{Estimated population}}}$$

where; calculated sample size = 150;estimated population = 100 then; n = 60 i.e. 30 in each arm.

From the study conducted at BPKIHS from March 2010 to August 2011, total no of patient with severe preeclampsia was 40 out of total delivery of 3959, that is about 100 patients can be taken in a year.

Keeping all these values the number comes to be about 60, i.e. 30 in each arm.

The data was collected and entered in Microsoft Excel software. Analysis was done using SPSS 16 software. Differences were considered significant when P value was less than 0.05.

RESULTS

All the baseline characteristics in both of the groups were comparable as shown (Table 1).

Table 1. Baseline characteristics.

Characteristics	Standard dose (Pritchard regimen) group	Single dose only group	P value
Age (years)	25.03 ± 5.7	24.57 ± 4.96	0.55
Gravida (multi/primi) in %)	30/70	37/63	0.58
Gestational age (weeks)	37.2 ± 4.11	37.1 ± 3.55	0.73
BP at admission (mm of Hg)	157.67 ± 23.73/110.33 ± 14.96	152.33 ± 20.95/102 ± 13.49	0.60/0.07
BP at Randomisation (mm of Hg)	159.67 ± 19.91/113 ± 11.49	161 ± 18.26/107.67 ± 11.94	0.79/0.27
Presented in labour at admission	26.7	46.7	0.10
Proteinuria > 2+ (%)	70	69.7	0.39
Deranged LFT (%)	20	16.7	0.74
Deranged RFT (%)	10	6.7	1.00
Low platelates($< 10^5$/cumm) (%)	13.3	10	1.00
Vaginal Delivery (%)	60	53.3	0.60
Caesarean Section (%)	40	46.7	0.60

In both groups, there was no maternal mortality and they were followed up till discharged from the hospital. Total of 3 patients developed seizure despite MgSO4 prophylaxis, 1 (3.3%) in standard dose and 2 (6.7%) in Loading dose only group (Table 2). All of them had only 1 episodes of seizure which was managed by 2 gm (20%) MgSO4 IV slowly followed by maintenance dose of magnesium sulfate four hourly up to 24 hrs of seizure. The occurrence of seizure is not significant statistically as P value was 1.00.

Total of 3 patients needed ICU care and 12 patients developed maternal complications. The maternal complications were seizure, Abruptio placentae, acute kidney injury, PPH, HELLP syndrome, Hyponatremia and ruptured uterus which were comparable.

Total of 17 (56.7%) patients in standard dose regimen and none in loading dose only regimen had MgSO4 toxicities (Table 2). Due to the toxicity maintenance dose had to be skipped. The mean number of skipped injections was 2.2 ± 2.18. Maximum number of skipped IM injections was 8. Mean duration of hospital stay in both groups were comparable 4.7 ± 1.54 and 4.2 ± 1.15 days respectively. Total number of IM injections of MgSO4 received was obviously higher in standard dose regimen than loading dose only, mean 7.57 ± 2.17 and 2.47 ± 1.79 respectively. The median number of skipped MgSO4 due to its toxicities in standard dose regimen was 3 ± 2.18.

Table 2. Maternal complications.

Characteristics	Standard Dose regimen	Loading dose only regimen	P value
	n (%)	n (%)	
No of patient transferred to ICU	2 (6.7)	1 (3.3)	1.00
Maternal complications	7 (23.3)	5 (16.7)	
Type of maternal complications (n = 12)			
Seizure	1 (8.3)	2 (16.6)	1.00
Abruptio placentae	1 (8.3)	1 (8.3)	
Acute kidney injury	1 (8.3)	1 (8.3)	
Hyponatremia	1 (8.3)	0	
PPH	1 (8.3)	1 (8.3)	
HELLP syndrome	1 (8.3)	0	
Ruptured Uterus	0	1 (8.3)	
	MgSO4 toxicity		
Characteristics	**Standard Dose regimen**	**Loading dose only regimen**	
	n (%)	n (%)	
MgSO4 toxicity	17 (56.7)	0	<0.001
Absent knee jerk	16 (53.3)	0	
Decreased urine output	5 (16.7)	0	
Mean duration of hospital stay (days)	4.77 (4.2)	0.11	
Mean no of IM MgSO4 received	7.57 (2.47)	<0.001	
Median no of skipped IM MgSO4	3	<0.001	

Perinatal Outcome at discharge: In standard dose regimen 73.3 percent baby were alive whereas in case of loading dose only regimen 93.3 percent of baby were alive after 48 hours of delivery (Table 3).

Table 3. Perinatal outcome.

Fetal outcome	Standard Dose	Loading dose only
	n (%)	n (%)
Alive	22 (73.3)	28 (93.3)
Fresh still birth	3 (10)	1 (3.3)
IUFD	3 (10)	1 (3.3)
NND	2 (6.7)	0
APGAR < 7 at 0	4 (n = 24) (16.7)	5 (n = 28) (17.9)
APGAR < 7 at 1 min	1 (n = 24) (4.2)	1 (n = 28) (3.6)
APGAR < 7 at 5 min	**0**	**0**

Similarly, about 20.83% in standard dose whereas 14.28% in loading dose only were admitted after delivery. However, birth weight in both of the groups was comparable. Low birth weight was present in 53.3 and 46.7 percent of cases respectively. Normal birth weight was equal in both groups (P = 0.79). The average birth weight was 1470 ± 507 grams and 1500 ± 504 grams for standard dose and loading dose only regimen respectively.

DISCUSSION

In both standard and loading dose only group primigravida accounted for majority of cases i.e. 70% and 63% respectively. This finding is similar to a study done by Darngawn L et al.[7]

In this study, mean systolic BP at randomization was 159.67 ± 19.91 and 161 ± 18.26 mm of Hg and mean diastolic BP 113 ± 11.49 and 107.67 ± 11.94 mm of Hg in the standard dose and loading dose respectively similar to the study done by Fontenot TM et al.[8] Majority (60%) of the cases in the standard dose and majority (63.3%) of the cases in loading dose only had systolic blood pressure of >160 mm of Hg. Similarly, majority (73.3%) of the cases in the standard dose and majority (60%) of the cases in loading dose had diastolic pressure of >110. This finding is different than the findings of the study conducted by Ranganna H et al. done at Chandigarh, India.[9]

In standard dose group 40% underwent Caesarean section whereas in loading dose 45.7% had Caesarean section. There was no significant difference in the mode of delivery in both groups. This finding is similar to the study conducted by Darngawn L et al in Vellore.[7] This finding was different than the study conducted by Shoaib T et al. done in Karachi, Pakistan where the rate of caesarean section was lower in loading dose 12% versus 30% in the standard dose.[10]

In both groups, there was no maternal mortality and they were followed up till discharged from the hospital. This finding is similar to the study conducted by Shoaib T et al. done in Karachi, Pakistan where no maternal death was observed in either group.[10] Similarly this finding is similar to the study conducted by Malapaka SVN et al. in Mangalore, India where no maternal mortality was observed in both groups.[11]

The present study clearly demonstrated that loading dose of magnesium sulfate is as effective as standard dose for the prevention of seizure with better maternal and fetal outcome and added further evidence to the findings by previous investigators. There was no significant difference in both groups in the term of occurrence of seizures. This finding is similar to the study conducted by Ranganna H et al. done at Chandigarh, India which reported only one case having seizure in both the group.[9] This finding is also similar to the study conducted by Shoaib T in which no significant difference was found in terms of occurrence of seizure.[10] In this study none in the loading dose and only one in the standard group developed seizure. This finding is also similar to the study conducted by Murthy KO et al. in Puducherry, India in which no one in the standard dose and only one in the low dose developed seizure.[12] This finding is also similar to the study carried out by Malapaka SVN et al. in Mangalore, India which reported that both the low dose MgSO4 was equally effective at preventing the occurrence of seizures among women with severe preeclampsia. In the study, no one of the cases experienced seizure.[11] A study conducted by Shah R et al. in Pune, India reported that single loading dose of Mgso4 is effective in preventing seizure which is similar to the findings of this study.[13]

In the present study, 6.7 % in the standard dose and 3.3% in the loading dose were transferred to the intensive care unit (ICU) for further care. In contrast, a study conducted by Fenn MG et al. in Tamilnadu, India reported 4% in the standard dose and 8% in low dose being admitted in ICU.[14]

In the current study, maternal complication was present in 23.3% in the standard dose and 16.7% in the loading dose only. This finding is different than a study conducted by Shoaib T in which no serious untoward effects were observed in either group.[10]

In the present study HELLP syndrome was observed in 3.3% of the cases in the standard dose. None of them in loading dose had HELLP syndrome. In terms of standard dose this finding is comparable with the study done by Ranganna H et al. done at Chandigarh, India in which 2% of the cases had HELLP syndrome in the standard dose. In terms of loading dose only the findings is different from this study as 4% of the cases had HELLP syndrome.[9] The findings revealed by the study done by Fenn MG is comparable in which 2% of the Pritchard group developed HELLP syndrome and no one developed HELLP syndrome in the loading dose.[14] This finding is different than the study conducted by Malapaka SVN et al. in Mangalore, India in which HELLP syndrome was observed in 12.5% and 2.7% of the cases in Pritchard group and low dose group respectively.[11]

In this study 3.3% from both the groups had acute renal failure. This is different than the study conducted by Fenn MG in Tamilnadu, India in which only 1% of the cases from both the group had acute renal failure.[1] This finding is different than the study conducted by Malapaka SVN et al. in Mangalore, India in which no one of them in both group developed acute renal failure.[11]

In the current study magnesium toxicity (absent/ sluggish knee jerk, decreased urine output, respiratory rate less than 16) was observed in most (56.7%) of the cases in the standard dose. None of the cases in loading dose developed magnesium toxicity which is similar to the study done by Ranganna H et al.[9]

In this study 16.7% in the standard dose and none in loading dose only group had oliguria. In contrast, study conducted by Fenn MG in Tamilnadu, India showed that 10% in the Pritchard group and 14% in low dose group developed oliguria.[14] This is also in contrast with the study done by Malapaka SVN et al. in Mangalore, India which reported majority (75%) having oliguria.[11] This finding is also different from the study conducted by Maia SB in Brazil in which none in the standard dose developed oliguria and 1.8% in the low dose group had oliguria.[15]

In the study, live birth was 80% and 93.3% in the standard dose and loading dose respectively. This finding is similar to the study conducted by Ranganna H et al. done at Chandigarh, India.[9] Still birth was found in 10% of the cases in standard group and 3.3% in the loading dose group. The study conducted by Malapaka SVN et al. in Mangalore, India reported that none of the cases in standard dose had stillbirth which is in contrast with this study and 2.7% in the low dose group had stillbirth which is comparable with the findings of our study.[1] The study conducted by Ranganna H et al. done at Chandigarh, India found 11.53% stillbirth in standard dose which is comparable to this study and 7.69 stillbirth in the loading dose which is in contrast to this study.[9]

In the present study, neonatal death (NND) was seen in 6.7% of the cases in the standard dose. There was no neonatal death in the loading dose. The study conducted by Malapaka SVN et al. in Mangalore, India reported that 6.3% of the cases in standard dose had NND which is similar with this study and 13.5% in the low dose group had NND which is in contrast with the findings of our study.[11]

About 20.83% of the babies in the standard dose and 14.28% of the babies in loading dose were admitted to neonatal care unit. The study conducted by Ranganna H et al. done at Chandigarh, India reported that 19.23% of the babies in the standard doses were admitted in standard dose which is similar to this study and 32.69% in loading dose were admitted which is different from this study.[9]

CONCLUSIONS

The present study provides evidence that single dose (loading dose only) of magnesium sulfate is equally effective as standard dose (Pritchard regimen) magnesium sulfate in terms of seizure prophylaxis in severe pre eclamptic women with better maternal outcome and neonatal outcome. There was no significant difference in both groups in the term of occurrence of seizures.

Conflict of Interest: None.

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