Journal of Indian Academy of Obstetrics and Gynaecology July 2020

Vol. 2, Issue 1

Original Article

MODIFIED PROPHYLACTIC MAGNESIUM SULFATE THERAPY IN SEVERE PRE-ECLAMPSIA - A RANDOMISED CONTROL STUDY

Anurag Mallick

ABSTRACT

Background - The primary aim of treatment in preeclampsia is to prevent eclamptic seizures, and resultant morbidity and mortality. Magnesium Sulfate has proved to be the optimal drug for seizure prophylaxis.

Methods: A randomized controlled trial for MgSO4 prophylaxis was conducted between July 2015 to June 2016. Randomization = Sequence generation - Computer generated random numbers. Allocation concealment mechanism - opaque sealed envelopes. Informed consent obtained, subjects were randomly assigned to any of the group. Intervention Group A – received MgSO4 for 8 hrs. Control Group B – received MgSO4 for 24 hrs.

Results: Out of 45 women in the intervention group A, magnesium sulphate was continued in only 1 woman beyond 8 hours (2.2) [$p < 0.001$]. The time that doctors spent monitoring the women was significantly less in the group A than in the control group B [$p < 0.001$]. Time spent by the nurses in giving MgSO4 injections and care thereafter was significantly less in the group A ($P<0.001$). Pain felt by the women due to MgSO4 injection was found to be significantly less in the group A ($P<0.001$), and women in the intervention group were better able to look after themselves. In group A significant reduction was observed in duration of postpartum Foley's catheter and time to early ambulation.

Conclusion: The abbreviated regime of is a suitable alternative to the traditional regime and is associated with less exposure to the drug, both in terms of duration and total dose but with similar clinical outcomes.

Key Words: severe pre-eclampsia, MgSO4 prophylaxis, eclampsia, abbreviated regime

Introduction: Pre-eclampsia, a pregnancy specific multisystem disorder, is characterized by the development of hypertension and proteinuria after 20 weeks of gestation [(1)]. Pre-eclampsia occurs in 2-8% of pregnancies [(2,3,4)]. An important complication of severe pre-eclampsia is eclampsia, which may occur prior to, during, or following delivery and is associated with an increased risk of maternal death [(5,6,7,8)]. The primary aim of treatment in preeclampsia is to prevent eclamptic seizures, and resultant morbidity and mortality. Magnesium Sulfate has proved to be the optimal drug for seizure prophylaxis [(10)]. Eclampsia can be prevented with magnesium sulfate, which decreases the risk of seizures by 50%, along with a reduction in maternal mortality [(2,11,12,13)]. Although magnesium sulfate administration is recommended for all women with severe pre-eclampsia [(13)], there is no consensus regarding the ideal duration of prophylactic postpartum anticonvulsant therapy [(14)].

Traditionally, the use of magnesium sulfate has been recommended for 24 hours following delivery, the period of greatest risk for the occurrence of eclampsia [(2,15)]. Nonrandomized studies have used clinical criteria for stopping magnesium sulfate earlier in some women with pre-eclampsia [(16,17)]. By reducing the duration of therapy, the frequency of monitoring maternal blood pressure and urinary output may be curtailed and early ambulation and care for her newborn may be increased. However, a systematic review [(18)] found that some women who received a short-duration magnesium sulfate treatment regimen required a prolongation or re-institution of therapy, although this finding was not statistically

significant. In economically developing nations like India, the use of magnesium sulfate is also effective [2]. However, unnecessarily prolonged use of magnesium for seizure prophylaxis in resource-constrained regions might delay a mother's return to normality and thus preclude such recommended practices as kangaroo care [19].

Materials and Methods

Study was done in the Department of Obstetrics and Gynaecology, R.G.Kar Medical College from 1st July 2015 to 30th June 2016 in Severe Stable Pre-eclamptic patients admitted in Department of Obstetrics and Gynaecology of RGKMCH. The study was Interventional Prospective Randomized Controlled Study. Purpose was intention to treat. Randomization and Sequence generation was done by Computer generated random numbers. Allocation concealment mechanism was through Opaque sealed envelopes. Once informed consent is obtained, subjects will be randomly assigned to any one of the intervention group. Intervention Group A received MgSO4 for 8 hrs. and Control Group B received MgSO4 for 24 hrs.

Severe pre-eclampsia was defined as a systolic blood pressure of 160 mm Hg or more and/or a diastolic blood pressure of 110 mm Hg. Pre-eclampsia was deemed to be "stable" in the absence of visual signs or symptoms (scotomata or blurred vision), frontal and/or occipital headache, hyperreflexia, and either epigastric or right hypochondrium pain. Women with eclampsia were excluded from the study, as were those with evident hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, pre-existing diabetes mellitus, epilepsy, renal disease, a contraindication to the use of magnesium sulfate such as known hypersensitivity to the drug, or anuric or oliguric urinary output under 25 mL/hour. All women were already receiving magnesium sulfate before and during delivery. Postpartum, all participants received an 8-hours of magnesium sulfate. Approximately 4 hours after delivery, eligible women were invited to participate in the trial. Those who provided written informed consent were enrolled and assigned a randomization number.

The participants were randomized 1:1 to receive an ongoing (24-hour) or abbreviated (8-hour) magnesium sulphate. Randomization was achieved using a sequential list of random numbers ranging from 1 to 45. The group allocation was concealed in opaque, sequentially numbered envelopes, which remained sealed until randomization. At 8 hours, after completion of the initial period of magnesium sulfate, each woman's study envelope was opened. If she was assigned to 24 hours of treatment, her MgSO4 was continued for another 16hours. If she was assigned to 8 hours of treatment, her $MgSO_4$ was stopped and normal saline was used. As a safety measure, in the rare situation where a woman was assigned to the abbreviated magnesium protocol and she had very high blood pressure (systolic blood pressure of 180 mm Hg or more and/or a diastolic blood pressure of 120 mm Hg or more), her urine output was under 25 mL/hour, and/or she had signs of imminent eclampsia, she was maintained on magnesium sulfate for the duration deemed necessary by her attending physician. These women were described as "need to continue magnesium sulfate treatment after 8 hours" and were not considered to belong to the abbreviated treatment group. In the 24-hour treatment group, the attending physician was also permitted to extend magnesium therapy if he/she deemed this to be necessary. Clinical and laboratory measures were assessed in both groups until at least 24 hours following delivery. The women were evaluated every 4 hours for heart rate, respiratory rate, blood pressure, and urine output. Deep tendon reflexes were evaluated every 4 hours and laboratory tests to screen for the HELLP syndrome were evaluated every 24 hours. At approximately 24 hours after delivery, each woman's satisfaction with her care was evaluated on a scale of 1–5.

(1 = very satisfied, 2 = satisfied, 3 = not very satisfied, 4 = dissatisfied, and 5 = very dissatisfied)

Laboratory investigations used for monitoring were Hb%, TC, DC, ESR, Platelet Count, Plasma Glucose level, Urea, Creatinine, Uric Acid, Liver Function Test, and Proteinuria.

STUDY VARIABLES

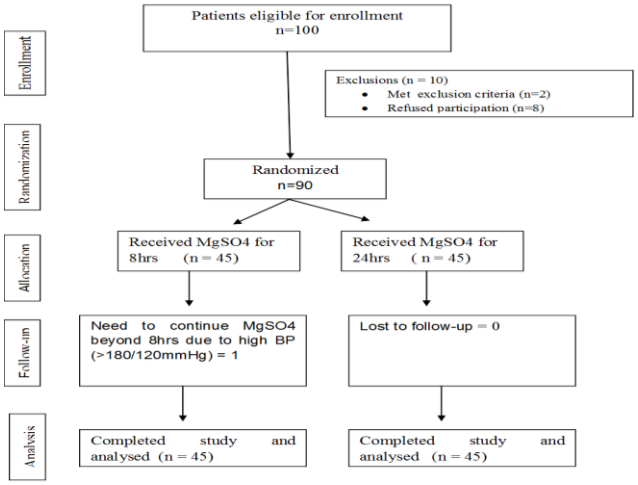
DEMOGRAPHIC	AGE RELIGION
OBSTETRIC	PARITY GESTATIONAL AGE AT DELIVERY MODE OF DELIVERY
CLASSIFICATION OF HYPERTENSION	SEVERE GESTATIONAL HYPERTENSION SEVERE PRE-ECLAMPSIA CHRONIC HYPERTENSION WITH SUPERIMPOSED PRE-ECLAMPSIA

INCLUSION CRITERIA	Post partum Women with Stable Severe Pre-Eclampsia
EXCLUSION CRITERIA	*HELLP Syndrome *Epilepsy *Class A2 Gestational Diabetes *Oliguria *Refused Participation

Sample size was calculated using SPSS 20.0. 1.Based on previous data [17], it was assumed that the mean duration of magnesium sulfate treatment in the abbreviated group would be 18 ± 9 hours, whereas women in the 24-hour treatment group would receive therapy for 24 ± 6 hours. To detect this 6-hour difference in the duration of treatment with a statistical power of 90% and a two-sided P value 0.05, 35 women were needed per group.

Considering possible drop-outs, the sample size was increased by 20%, resulting in a total of 45 women per group (total 90).

PATIENTS FLOW DIAGRAM



Results

During the study period from July 2015 to June 2016, a total of 100 women were approached but 10 women were excluded as 8 of them refused to participate, one was a known case of Epilepsy and another one was also a known case of gestational diabetes. Of the remaining 90 women who fulfilled the eligibility criteria, 45 were randomized to receive magnesium sulphate for 8hours and 45 were randomized to receive magnesium sulphate for 24hours. Among the women randomized to receive MgSO4 for 8hours, one woman had to continue MgSO4 beyond 8hours because of persistent hypertension (BP >180/120 mmHg). She received 10mg Nifedipine orally and her blood pressure dropped to 166/110 mmHg after 45 minutes. Thus, the intramuscular regime was continued up to 24hours.

Baseline variables such as age, gestational age at delivery, parity, and mode of delivery were comparable in both groups. (Table 1) Most clinical and laboratory parameters like Heart Rate, Respiratory Rate, Platelet Count, Creatinine, Uric acid, Serum LDH, AST (Aspartate Aminotransferase), Total Bilirubin at admission were similar, with no differences in the severity of the disease. (Table 1)

During the study, no statistically significant differences were found between the groups with respect to blood pressure or urine output. None of the women had to interrupt anticonvulsant therapy because of adverse effects of the drug. There were no occurrences of eclampsia, acute pulmonary edema, thromboembolic complications, kidney failure, liver failure, disseminated intravascular coagulation, cerebrovascular accidents or maternal deaths. Minor complications like urinary tract infection were found statistically significant among the women receiving MgSO4 for 24hours. The duration of anti-convulsant therapy was significantly shorter among the women receiving Magnesium sulphate for 8hoursresulting in reduction of total dose of Magnesium sulphate.

The total duration of indwelling urinary catheter use was also significantly shorter in the group of women receiving MgSO4 for 8hours. Similar results with significant reduction in time from delivery to ambulation were seen among the women receiving MgSO4 for 8 hours. A significant reduction in time from delivery to contact with the newborn infant was also found in the abbreviated regime (8 hours) group. Monitoring time by doctors, time required for nursing care and for injections was significantly reduced among the women receiving MgSO4 for 8 hours (Table 2).

Discussion: In the present study, Magnesium sulphate was continued for only 1 woman beyond 8 hours, out of 45 women (2.2%) in the intervention group [$p < 0.001$]. In a study of 503 women, Isler et al. [16] used clinical symptoms to guide postnatal MgSO4 therapy, and reported a 7.6% need for reinstitution of MgSO4. A more recent randomized controlled trial by Ehrenberg et al. [20] examined disease progression during a 12-hour and 24-hour postpartum MgSO4 regime for mild pre-eclampsia, and reported the need to extend MgSO4 administration among 6.9% of women in the 12-hour group.

In a randomized control trial by Darngawn et al [21]. comparing a shortened 6 hours magnesium sulphate prophylaxis regime versus 24 hours in pre-eclamptic women at low risk of eclampsia, only one woman out of 75 (1.3%) in the 6hours intervention group needed to continue magnesium sulphate because of worsening hypertension nine hours following delivery.

Regarding the secondary outcomes, no eclampsia occurred in either group, a finding consistent with those of Isler et al. [16] and Ascarelli et al. [17].

The time that doctors spent monitoring the women was significantly less in the intervention group (8 hours group) than in the control group (24 hours group) [P<0.001].

Similarly, time spent by the nurses in giving MgSO4 injections and care thereafter was significantly less in the intervention group (P<0.001). Intramuscular injections are associated with a lot of pain at the injection site; thus, it is our standard practice to mix MgSO4 with 2% xylocaine. The resultant 10 mL of preparation can cause abscesses; so, hot fomentation is applied to the injection site after each injection. The time saved by shortening the MgSO4 regime would be of great significance in low-resource countries such as India, which has a nurse-to-patient ratio of 1:4 and a doctor-to-patient ratio of 1:5. [21]

Table 1. COMPARISON OF BASELINE CHARACTERISTICS

VARIABLES	GROUP A (n=45)	GROUP B (n=45)	p VALUE
AGE [Mean (SD)]	19.84 (2.66)	19.93 (2.38)	0.8680
PARITY [n (%)] PRIMIPARA MULTIPARA	33 (73.3) 12 (26.7)	39 (86.7) 6 (13.3)	0.1183
GESTATIONAL AGE AT DELIVERY [Mean (SD)]	35.85 (0.89)	35.79 (0.94)	0.7487
Types of Hypertension[n(%)] Chronic HTN Gestational HTN Pre-Eclampsia	1 (2.2) 2 (4.4) 42(93.3)	1 (2.2) 1 (2.2) 43(95.6)	0.8415
MODE OF DELIVERY [n(%)] C-Section Instrumental Normal	36 (80) 2 (4.4) 7 (15.6)	33 (73.3) 3 (6.7) 9 (20)	0.7481
HEART RATE [Mean (SD)]	86.44 (3.69)	86.57 (4.48)	0.8780
RESPIRATORY RATE [Mean (SD)]	15.88 (1.55)	16.02 (1.33)	0.6641
URINE OUTPUT (in ml/hr) [Mean (SD)]	81.88 (15.56)	81.22 (15.78)	0.8406
PLATELET COUNT (in lakhs/cmm) [Mean (SD)]	2.08 (0.21)	2.14 (0.26)	0.2425
SERUM CREATININE (mg/dl) [Mean(SD)]	0.51 (0.08)	0.53 (0.07)	0.3861
URIC ACID (mg/dl) [Mean (SD)]	5.19 (0.36)	5.21 (0.40)	0.7873
SERUM LDH (U/L) [Mean (SD)]	265.64 (8.70)	264.04 (8.79)	0.3880
AST (U/L) [Mean (SD)]	23.20 (4.74)	23.00 (4.30)	0.8345
TOTAL BILIRUBIN (mg/dl) [Mean (SD)]	0.44 (0.16)	0.46 (0.17)	0.6165

TABLE 2. COMPARISON OF OTHER SECONDARY VARIABLES

VARIABLES	GROUP A (n=45)	GROUP B (n=45)	p VALUE
MONITORING TIME BY DOCTORS (in minutes) [Mean(SD)]	20.00 (0.82)	30.46 (1.14)	<0.0001
INJECTION TIME (in minutes) [Mean (SD)]	6.77 (2.17)	18.46 (1.14)	<0.0001
NURSING CARE TIME (in minutes) [Mean (SD)]	32.40 (1.72)	88.88 (6.09)	<0.0001
NEED TO CONTINUE MgSO4 BEYOND 8HRS [n(%)]	1 (2.2)	45 (100)	<0.0001
MINOR COMPLICATIONS [n(%)]	10 (22.2)	25 (55.6)	0.001

Pain felt by the women due to MgSO4 injection was found to be significantly less in the intervention group than in the control group (P<0.001), and women in the intervention group were better able to look after themselves.

A significant reduction was found in the duration of postpartum indwelling urinary catheter use, which may account for the reduction in the risk of urinary tract infection [(22)] and the decrease in postpartum discomfort reported by the women in women receiving MgSO4 for 8 hours.

A reduction was found in the time to ambulation with the shorter regimen of postpartum magnesium sulfate. Early ambulation is important for the prophylaxis of deep vein thrombosis [(23)]. The shorter, 8hours magnesium sulfate therapy enables women to benefit from this prophylactic practice.

Another benefit associated with shorter magnesium sulfate therapy was the possibility of earlier contact with the newborn, improving the likelihood of establishing breastfeeding. It is common practice during magnesium sulfate administration for the woman to remain in an intermediate or intensive care unit, which may contribute towards preventing the mother from breastfeeding her infant. In the present study, a significant reduction was found in the time from delivery until contact with the newborn in the 8-hour group.

Moreover, more well-designed studies should be conducted with larger sample sizes to avoid hasty conclusions based on a single study.

Conclusion

In our study, time from delivery to ambulation, Time from delivery to contact with newborn infant, Duration of indwelling urinary catheter use, Time spent by doctors for monitoring, Time spent by nurses for giving injections and associated care and minor complications like urinary tract infections was significantly less in the women receiving magnesium sulphate for 8 hours than those women receiving for 24 hours. There is also reduction in total dose of Magnesium sulphate and the pain relief or satisfaction of the patients were significantly more in the women receiving Magnesium sulphate for 8hours than those receiving for 24 hours.

Limitations

The study has some limitations. First, eclampsia was not taken as the primary outcome because of its low incidence (0.5% to1.8%) in India [(25)], of which only a quarter occurs in the postpartum period. In addition, we did not monitor the effects of the regime co-morbidity by any of known scales of morbidity. Although not powered to detect the difference of the incidence of Eclampsia, the present randomized control trial indicates that the abbreviated (8 hours) regime of postpartum Magnesium sulphate for seizure prophylaxis is a suitable alternative to the traditional (24 hours) regime and is associated with less exposure to the drug, both in terms of duration and total dose but with similar clinical outcomes. So, a larger number of women with Pre-eclampsia should be studied to come to a robust conclusion about the abbreviated postpartum Magnesium sulphate regime.

Conflict of interest: Authors declare that they have no conflict of interest.

Ethical Approval: Institutional ethical committee clearence was obtained.

Acknowledgements: Dr. Shyamal Dasgupta, Associate Professor, R.G.Kar Medical College, Kolkata.

References

1. Wagner LK. Diagnosis and management of preeclampsia. *Am Fam Physician* 2004; 70(12):2317–24.
2. WHO Library Cataloguing-in-Publication Data. WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia. WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf. Published 2011
3. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010; 376(9741): 631–44.
4. Duley L. The global impact of pre-eclampsia and eclampsia.*SeminPerinatol* 2009; 33(3):130–7.
5. Sibai BM. Diagnosis, prevention, and management of eclampsia. *ObstetGynecol* 2005; 105(2):402–10.
6. Kullima AA, Kawuwa MB, Audu BM, Usman H, Geidam AD. A 5-year review of maternal mortality associated with eclampsia in a tertiary institution in northern Nigeria. *Ann Afr Med* 2009; 8(2):81-4.
7. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomized trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at 2 years. *BJOG* 2007; 114(3):300–9.
8. Khan KS,Wojdyla D, Say L, Gülmezoglu AM, Van Look PF.WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; 367(9516):1066–74.
9. Amorim MMR, Katz L, Ávila MB, Araújo DE, Valença M, Albuquerque CJM, et al. Admission profile in an obstetric intensive care unit in a maternity hospital of Brazil.*Rev Bras SaúdeMatern Infant* 2006;6(1):S55–62.
10. Altman D, Carroli G, Duley B, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised, placebo-controlled trial. *Lancet* 2002;359(9321):1877–90.
11. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010; 11:CD000025.

12. Noronha Neto C, de Souza ASR, Amorim MMR. Pre-eclampsia treatment according to scientific evidence. *Rev Bras GinecolObstet* 2010; 32(10):459–68.
13. ACOG Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002; 99 (1) :159–67.
14. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J ObstetGynecol* 2004; 190(6):1520–6.
15. World Health Organization.Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors.
http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf.Published 2003.Accessed February 4, 2012.
16. Isler CM, Barrilleaux PS, Rinehart BK, Magann EF, Martin Jr JN. Postpartum seizure prophylaxis: using maternal clinical parameters to guide therapy. *ObstetGynecol* 2003; 101(1):66–9.
17. Ascarelli MH, Johnson V, May WL, Martin RW, MartinJr JN. Individually determined postpartum magnesium sulfate therapy with clinical parameters to safely and cost-effectively shorten treatment for pre-eclampsia. *Am J ObstetGynecol* 1998; 179(4):952–6.
18. Duley L, Matar HE, Almerie MQ, Hall DR. Alternative magnesium sulphate regimens for women with pre-eclampsia and eclampsia. *Cochrane Database Syst Rev* 2010; 4: CD007388.
19. Conde-Agudelo A, Belizan JM, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2011;3: CD002771.
20. Ehrenberg HM, Mercer BM. Abbreviated postpartum magnesium sulfate therapy for women with mild preeclampsia: a randomized controlled trial. *ObstetGynecol* 2006; 108(4):833–8.
21. Darngawn L, Jose R, Regi A, Bansal R, Jeyaseelan L. A shortened postpartum magnesium sulfate prophylaxis regime in pre-eclamptic women at low risk of eclampsia. *Int J GynecolObstet* 2012; 116(3):237–9.
21. Darngawn L, Jose R, Regi A, Bansal R, Jeyaseelan L. A shortened postpartum magnesium sulfate prophylaxis regime in pre-eclamptic women at low risk of eclampsia. *Int J GynecolObstet* 2012; 116(3):237–9.
22. Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters.*Emerg Infect Dis* 2001;7(2):342–7.
23. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines* (8th Edition). Chest 2008; 133 (6 Suppl.): 844S–86S.
24. Bhargava A, Pant R, Nimmi C, Singh SK. In search of accelerated recovery from eclampsia. *J ObstetGynecol India* 2006;56(5):402–5.
25.Maia SB, Katz L, Noronha NC, Caiado BVR, Azevedoana PRL, Amorim MR, et al. *Int J Gynecol and Obstet* 2014; 126:260-264

ABBREVIATIONS:
MgSO4 - Magnesium Sulphate
HRS - Hours
HTN - Hypertension
C- section - Caesarean Section
LDH - Lactate Dehydrogenase
AST - Aspartate Transaminase

Received: 26th September 2019
Accepted: 10th January 2020
Published online: 1st July 2020
Citation: Mallick A. Modified prophylactic magnesium sulphate therapy in severe pre-eclampsia - a randomised control study. J Indian Acad Obstet Gynecol 2020; 2(1): 7-12

40, ARABINDA NAGAR, KOLKATA – 700104
✉ EMAIL ID – mallickanurag47@gmail.cor