Original Article

Abbreviated 12-Hour Postpartum Magnesium Sulphate Therapy is Equally Effective and Safer Than Standard 24-Hour Therapy in Preeclampsia With Severe Features: Results From A Randomized Controlled Trial

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Abstract

Objective: Eclampsia is a major life-threatening complication of preeclampsia with severe features leading to significant perinatal and maternal mortality and morbidity. Magnesium sulphate ($MgSO_4$) is the first-line therapy for eclampsia prevention and treatment, however, its use is associated with serious adverse effects and there is no consensus on the optimal duration of its therapy. This study compares the efficacy and safety of abbreviated 12-hour versus standard 24-hour $MgSO_4$ therapy during postpartum in patients having preeclampsia with severe features.

Materials and methods: Patients having preeclampsia with severe features were randomized 1:1 into the 12-hour and 24-hour groups. Modified Pritchard regimen was used. The primary outcome was the incidence of seizures. Secondary outcomes included serious maternal morbidity and other adverse effects associated with $MgSO_4$ use. Perinatal outcomes were also recorded. Analyses were intention-to-treat.

Results: A total of 116 patients [57 (12-hour group) and 59 (24-hour group)] were included. The mean age was 25(±4) years, while the mean gestation period was 34 (±4) weeks. The incidence of seizures was comparable in the two groups [1 (2%), 3 (5%), p=0.62]. Patients in the 12-hour group [1 (2%)] had lesser postpartum drowsiness compared to the 24-hour group [15 (25%), p<0.001] and consequently, lesser problems in breastfeeding [1 (2%) versus 10 (17%), p=0.008]. There were no inter-group differences in other adverse effects including loss of reflexes, oliguria, respiratory depression, and proportion of patients requiring interruption of therapy. Perinatal outcomes were also similar.

Conclusion: In patients having preeclampsia with severe features, 12-hour postpartum $MgSO_4$ therapy is equally effective in preventing eclampsia and has lesser postpartum drowsiness and problems with breast feeding compared to the standard 24-hour therapy.

Keywords: Eclampsia; Magnesium Sulphate; Pre-Eclampsia

Introduction

Hypertensive disorders are frequently encountered problems in pregnancy which can present in varying degrees of severity, ranging from gestational hypertension to preeclampsia with severe features and eclampsia. They are reported in ~10% of pregnancies globally (1, 2), with preeclampsia

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occurring in 2-8% of pregnancies. They lead to significant perinatal and maternal mortality and morbidity, being responsible for 10-15% of all maternal deaths in developing countries (1-4). At our tertiary care centre, the prevalence of hypertensive disorders in pregnancy is estimated to be nearly 20-25%, while that of preeclampsia and eclampsia is 12.8% and 1.5%, respectively (unpublished data). Much of the morbidity and mortality due to these disorders is related to eclampsia, which is a major obstetric emergency characterized by maternal seizures and requires expeditious management with magnesium sulphate ($MgSO_4$) (5). $MgSO_4$ is also used for seizure prophylaxis in patients having pre-eclampsia with severe features, since it has a high propensity to culminate in eclampsia. A rapid onset of action, absence of maternal and neonatal sedation, and a wide safety margin make it an ideal drug for use in this setting. The most common regimens of $MgSO_4$ in current use- the Pritchard's intramuscular (IM) regimen and Zuspan and Sibai's intravenous (IV) regimen- are of standard 24-hour duration after delivery or after last fit (6-8). However, the use of $MgSO_4$ comes with many adverse effects, some of which are dose-related. It is currently unclear whether reducing the duration of postpartum $MgSO_4$ use has any effect on its efficacy or safety (9). Thus, this randomized controlled trial (RCT) was done to investigate the comparative efficacy (in terms of maternal and fetal outcomes) and safety of abbreviated postpartum $MgSO_4$ therapy (12 hours) versus traditional 24-hour therapy (modified Pritchard regimen) in patients with preeclampsia with severe features.

Materials and methods

Study design, setting, and population: This open-label, active (parallel-group) RCT was done in the Department of Obstetrics and Gynecology of an apex, tertiary care referral center in North India and included pregnant women with preeclampsia with severe features admitted in the labour wards. Preeclampsia with severe features was defined by any of systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥110 mm Hg, thrombocytopenia (platelet count $<100 \times 10^9$/L), abnormal liver function (elevated liver enzymes above twice the upper limit of normal), serum creatinine >1.1 mg/dL or doubling after excluding other renal diseases, new-onset headache or visual disturbances, or pulmonary edema (10). Written consent was sought from all participants to participate in the study. Exclusion criteria were women who had an eclamptic seizure at the time of enrollment, contraindications for $MgSO_4$ use such as drug hypersensitivity, oliguria or anuria, coma, intracranial bleeding, myasthenia gravis, pulmonary edema, or those who had received either $MgSO_4$, phenytoin or diazepam pre-admission. The study was approved by the Ethics Review Committee (Intramural) of the Postgraduate Institute of Medical Education and Research, Chandigarh (NK/572/Res/2869A). Principles outlined in the Declaration of Helsinki were adhered to. Trial registration was done on the Clinical Trials Registry of India (CTRI/2016/07/007076).

Randomization, allocation concealment, and details of intervention(s): Eligible patients were randomized 1:1 into two groups according to the random numbers table. Allocation concealment was done using sequentially numbered opaque sealed envelopes, which were opened only after consent had been taken. The patients and the treating physicians were not blinded to the group allocation. At the time of randomization, all patients received IM modified Pritchard regimen i.e. loading dose of 12 g $MgSO_4$ [4 g IV (20% w/v) slowly over 4-5 minutes and 4 g (50% w/v) IM in each buttock] followed by 4g (50% w/v) IM in alternate buttock every 4 hours. In case of thrombocytopenia or coagulopathy, patients received the IV Zuspan regimen i.e. loading dose of 4g $MgSO_4$ (20% w/v) IV slowly 4-5 minutes followed by 1 g/hour IV maintenance infusion. In the intervention group (abbreviated 12-hour treatment), patients received $MgSO_4$ up to 12 hours after delivery, whereas in the control group (standard 24-hour treatment), $MgSO_4$ was given up to 24 hours after delivery.

Study procedures: A detailed physical examination (including obstetric examination) was done for all patients. Blood samples were taken for complete blood count, liver and kidney function tests, and coagulogram. Close monitoring was done peripartum for at least 24 hours post-delivery including hourly assessment of vitals and urine output, and four hourly assessments of deep tendon reflexes. Before giving each IM dose of $MgSO_4$, the presence of knee jerk, respiratory rate of more than 16/min, and urine output of more than 100 ml in the preceding 4 hours was ensured. For the IV regimen, these parameters were monitored every hour. $MgSO_4$ was discontinued if any of these parameters were affected and restarted once all three parameters were

normal. If the patient had eclamptic fits after enrolment, $MgSO_4$ was given as per standard guidelines and continued till 24 hours post-delivery or after the last fit, whichever was later. Antihypertensive therapy was titrated as per blood pressure records.

Study outcomes: The primary outcome was the proportion of patients who developed eclampsia. Secondary outcomes studied were serious maternal morbidity (respiratory depression or arrest, cardiac arrest, renal/liver failure, or pulmonary edema), other side effects of $MgSO_4$ such as postpartum drowsiness, loss of knee jerk, oliguria and confusion, and proportion of patients requiring stoppage or reduction of treatment. Perinatal outcomes like birth weight and Apgar scores at 1 and 5 minutes were noted.

Statistical analysis: Statistical Package for Social Sciences (SPSS) version 26 was used for analysis. Normality was assessed using Kolmogorov-Smirnov test. If normally distributed, continuous variables were summarized as mean (SD) and assessed using the Student's t-test, whereas for skewed distribution, median (range) was used, and comparison was done with the Mann-Whitney U test. Categorical variables were summarized as proportions and analyzed using the chi-square or Fisher's exact test. A $p<0.05$ was used to define statistical significance. Using the incidence rates of eclampsia of 0.1% and 10% in the two groups, a sample size of 120 (60 in each group) was arrived at for a power of 70% and an alpha error of 0.05.

Results

A total of 116 pregnant women with preeclampsia with severe features were included -57 in the 12-hour group and 59 in the 24-hour group (Figure 1).

Baseline demographics, clinical and laboratory characteristics

The mean age of women was 26 (4) years in the abbreviated 12-hour group and 25 (4) years in the 24-hour group. The mean gestational age at the time of delivery was 34 (4) weeks in both groups; most were primigravida [32 (58%) and 38 (68%), respectively, in the two groups]. The mode of delivery was vaginal in 34 (58%) patients in the standard 24-hour group and 30 (53%) patients in the abbreviated 12-hour group (p=0.71). Mean systolic blood pressure at admission was 158 (19) mm Hg and 150 (20) mm Hg, while the mean admission diastolic blood pressure was 105 (12) mm Hg and 99 (13) mm Hg, respectively, in the two groups. About one-half of the patients in each group had pedal edema at enrollment (Table 1).

Table 1: Baseline demographic and clinical characteristics

Parameter	12 hr	24 hr	p-value
Age, years	26 (4)	25 (4)	0.35
BMI, kg/m^2	26.4 (8.1)	26.1 (5.2)	0.84
POG, weeks	34.0 (3.6)	34.4 (3.8)	0.51
Primigravida, n (%)	32 (58%)	38 (68%)	0.56
SBP at admission, mm Hg	158 (19)	150 (20)	0.06
DBP at admission, mm Hg	105 (12)	99 (13)	0.06
Pedal edema, n (%)	31 (55%)	31 (52%)	0.85

Data represented as mean (SD) or n (%)
BMI= body mass index, DBP= diastolic blood pressure, POG= period of gestation, SBP = systolic blood pressure

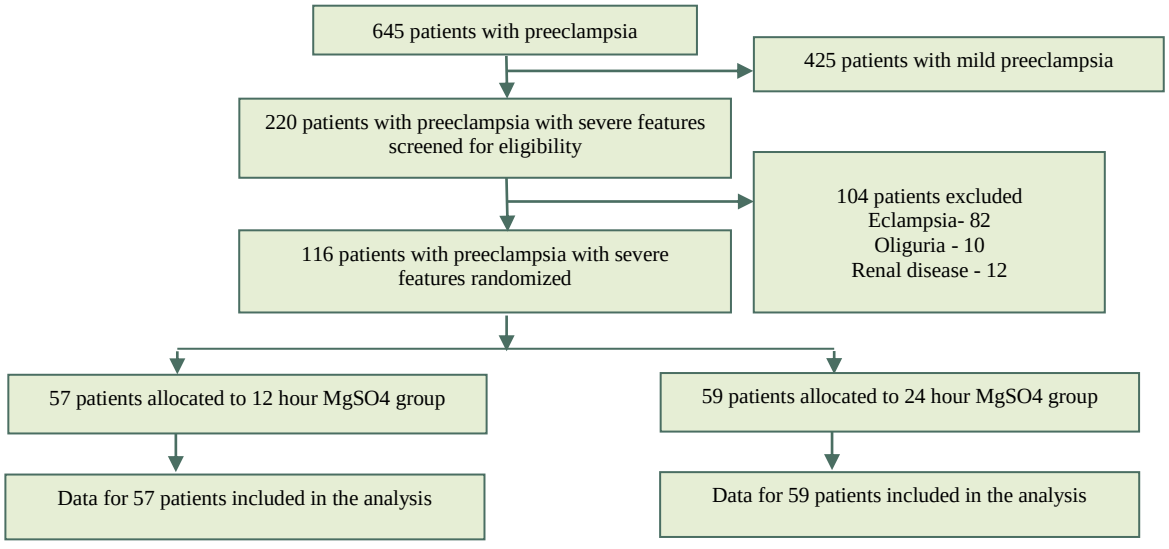

Figure 1: CONSORT flow chart

There were no differences in body mass index (BMI), hemoglobin, platelet count, transaminases, creatinine, and urine dipstick proteinuria between the groups (Table 2). Four (3.4%) patients (two in each group) received the IV $MgSO_4$ regimen.

Table 2: Baseline laboratory characteristics

Parameter	12 hr	24 hr	p-value
Hemoglobin, g/dL	11.5 (1.6)	11.0 (1.6)	0.11
Platelets, x 1000/uL	163 (67)	179 (77)	0.22
Creatinine, mg/dL	0.6 (0.2-6.5)	0.5 (0.1-1.3)	0.49
AST, U/L	41 (12-256)	52 (15-625)	0.56
ALT, U/L	50 (9-218)	49 (10-680)	0.75
Urine protein (dipstick)			0.30
Nil	12 (21%)	22 (37%)	
1+	16 (28%)	12 (20%)	
2+	15 (26%)	10 (17%)	
3+	10 (18%)	13 (22%)	
4+	3 (5%)	2 (3%)	

Data represented as mean (SD) or median (range) (as appropriate) and n (%)
ALT= alanine transaminase, AST= aspartate transaminase

Efficacy

There was no difference in the incidence of emergent seizures in the two groups -three (5%) patients in the traditional 24-hour group and one (2%) patient in the abbreviated 12-hour group developed seizures (p=0.62). No deaths were reported in either of the two groups (Table 3).

Table 3: Primary and secondary outcomes

Outcome	12 hr	24 hr	p-value
Occurrence of seizures, n (%)	1 (2)	3 (5)	0.62
Postpartum drowsiness, n (%)	1 (2)	15 (25)	<0.001
Problems in breast feeding, n (%)	1 (2)	10 (17)	0.008
Loss of knee jerk, n (%)	30 (54)	37 (63)	0.45
Oliguria, n (%)	2 (4)	1 (2)	1
Respiratory depression, n (%)	1 (2)	0	1
Confusion, n (%)	0	1 (2)	1
Abbreviation of infusion protocol due to complications, n (%)	28 (49)	31 (53)	0.71

Adverse effects

None of the patients developed serious maternal morbidity including respiratory or cardiac arrest, renal or hepatic failure, or pulmonary edema. However, postpartum drowsiness was more in the traditional 24-hour group [15 (25%) versus 1 (2%), p<0.001] leading to difficulty in breastfeeding neonates [10 (17%) versus 1 (2%), p=0.008]. Other adverse effects including loss of knee jerk, oliguria, respiratory depression, and confusion were similar in the two groups (Table 3). The proportion of patients requiring interruption of therapy due to adverse effects was also similar.

Perinatal outcomes

The birth weight and Apgar scores at 1 and 5 minutes were similar in babies born to mothers in both groups (Table 4). The mean birth weight in the two groups was 1.8 (0.8) kg and 2.0 (0.8) kg, respectively (p=0.32).

Table 4: Perinatal outcomes

Outcome	12 hr	24 hr	p-value
Baby weight, kg	1.84 (0.76) (n=52)	2.00 (0.82) (n=43)	0.32
Apgar score (1 minute)	6.0 (3.1) (n=52)	6.3 (2.9) (n=50)	0.71
Apgar score (5 minute)	7.6 (3.1) (n=52)	7.9 (2.7) (n=50)	0.43

Data represented as mean (SD)

Discussion

Although $MgSO_4$ forms the first-line therapy for the prophylaxis of seizures in preeclampsia, consensus is lacking on the optimal duration of postpartum $MgSO_4$ prophylaxis in preeclampsia with severe features (9, 11). Since $MgSO_4$ use is associated with potentially significant adverse effects, attempts have been made to reduce cumulative drug exposure either through the use of lower doses or for shorter durations (11-13). This parallel-group RCT compared the efficacy and safety of abbreviated 12-hour versus traditional 24-hour $MgSO_4$ in patients with preeclampsia with severe features and found that the abbreviated regimen is equally efficacious in terms of preventing the development of eclampsia and leads to fewer adverse effects in the form of lesser postpartum drowsiness and consequently, lesser problems with breastfeeding. In addition, the abbreviated regimen is cost-effective, requires lesser monitoring, and decreases the need for nursing care for neonates, which in turn saves resources and confers a significant advantage in developing countries. It also facilitates earlier mother mobilization and a consequent improvement in neonatal care.

Our findings are in line with the results of the large MOPEP study which compared 12-hour versus 24-hour $MgSO_4$ IM regimen (14). Although the MOPEP authors concluded that the 12-hour group had fewer adverse effects, these were limited to injection-site local complications, whilst the incidence of clinically significant adverse effects like

postpartum drowsiness, confusion, and loss of reflexes were notably similar in the two groups. Our study had slight methodological differences with the MOPEP study as the latter included patients with both eclampsia and preeclampsia with severe features (while we included patients with preeclampsia with severe features only) and the primary outcome evaluated was the occurrence of fits after treatment completion (while we reported occurrence of eclamptic fit any time after starting of therapy as our primary outcome) (14).

Similar findings were seen even with IV $MgSO_4$ use in two small RCTs conducted in Nigeria which compared 12-hour versus 24-hour IV maintenance $MgSO_4$ in pregnant females with pre-eclampsia with severe features alone (15) or both preeclampsia with severe features and eclampsia (16) and found similar efficacy in terms of incidence of eclampsia or recurrent seizures. However, the rates of postpartum drowsiness noted in these studies were not different in the two groups, in contrast to our study where post-partum drowsiness was higher in the 24-hour group. Whether this observed difference is due to different routes of $MgSO_4$ administration (IV versus IM) or reflects an ethno-geographic difference in propensity for $MgSO_4$-related adverse effects is uncertain and warrants exploration in further studies.

A recent meta-analysis of six studies comparing a single loading dose of $MgSO_4$ with the standard 24-hour regimen found similar efficacy of single-dose regimen in preventing the occurrence or recurrence of seizures with lesser incidence of loss of knee jerk (13). Although postpartum drowsiness was not studied as an outcome in this review, it does raise a possibility of further dose reduction of $MgSO_4$ beyond the 12 hours examined in the present study.

Our study indeed suffers from certain limitations - the sample size was relatively small and data on serum magnesium levels were not available. Further studies with a larger sample size targeting lower doses and/or shorter durations of $MgSO_4$ and overcoming the limitations of the present study are needed to find out the optimal dose and duration of $MgSO_4$ therapy for preventing eclampsia in patients having preeclampsia with severe features.

Conclusion

In patients with preeclampsia with severe features, an abbreviated 12-hour IM regimen of $MgSO_4$ is equally efficacious in terms of prevention of eclampsia when compared to the standard 24-hour modified Pritchard regimen, and leads to fewer adverse effects in the form of lesser postpartum drowsiness and consequently lesser problems with breastfeeding. A shorter regimen is also cost-effective, saves resources, and aids faster maternal mobilization for neonatal care.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

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References

1. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009, 33:130-7.
2. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. (2011). Accessed: 29 May 2024: https://apps.who.int/iris/rest/bitstreams/53238/retrieve.
3. Adu-Bonsaffoh K, Oppong SA, Samuel OA. Maternal deaths attributable to hypertensive disorders in a tertiary hospital in Ghana. Int J Gynaecol Obstet. 2013, 123:110-3.
4. Acquah-Arhin R, Kwawukuwe EY. Trends in eclampsia at Korle BU Teaching Hospatal, Accra Ghana. Nigerian Journal of Clinical Practice. 2003, 6:1-4.
5. Narkhede AM, Karnad DR. Preeclampsia and Related Problems. Indian J Crit Care Med. 2021, 25(Suppl 3):S261-S266.
6. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol. 1984, 148:951-63.
7. Zuspan FP. Problems encountered in the treatment of pregnancy induced hypertension. A point of view. Am J Obstet Gynecol. 1978, 131:591-7.
8. Sibai BM, Lipshitz J, Anderson GD, Dilts PV Jr. Reassessment of intravenous MgSO4 therapy in preeclampsia-eclampsia. Obstet Gynecol. 1981 Feb;57(2):199-202.
9. Okonkwo M, Nash CM. Duration of Postpartum Magnesium Sulphate for the Prevention of Eclampsia: A Systematic Review and Meta-analysis. Obstet Gynecol. 2022, 139(4):521-528.
10. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013, 122(5):1122-1131.

11. Yifu P, Lei Y, Yujin G, Xingwang Z, Shaoming L. Shortened postpartum magnesium sulfate treatment vs traditional 24h for severe preeclampsia: a systematic review and meta-analysis of randomized trials. Hypertens Pregnancy. 2020, 39(2):186-195.
12. Smith JM, Lowe RF, Fullerton J, Currie SM, Harris L, Felker-Kantor. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. BMC Pregnancy Childbirth. 2013, 13:34:1-11.
13. Salvador DAC, Salvador FC. Single loading dose versus standard 24-hour magnesium sulfate in women with severe preeclampsia and eclampsia: A systematic review and metaanalysis. Philipp J Obstet Gynecol. 2018, 42(5):1-10.
14. Beyuo TK, Lawrence ER, Kobernik EK, Oppong SA. A novel 12-hour versus 24-hour magnesium sulfate regimen in the management of eclampsia and preeclampsia in Ghana (MOPEP Study): A randomized controlled trial. Int J Gynaecol Obstet. 2022, 159: 495-504.
15. Unwaha EA, Bello FA, Bello OO, Oladokun A. Intravenous magnesium sulfate in the management of severe pre-eclampsia: A randomized study of 12-hour versus 24-hour maintenance dose. Int J Gynaecol Obstet. 2020, 149:37-42.
16. Grillo EO, Awonuga DO, Dedeke IOF, Abiodun O, Imaralu JO, Sotunsa JO et al. Comparison of Zuspan regimen and its 12-hour modification in women with severe pre-eclampsia and eclampsia in two hospitals in Abeokuta. Pregnancy Hypertens. 2023, 32:22-27.

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