Comparison of Loading Dose of MgSO4 Versus Standard Regimen in Severe Pre-Eclampsia in Pregnant Women from Swat, Pakistan: A Randomized Clinical Trial

Journal of Health and Rehabilitation Research (2791-156X)
Volume 4, Issue 3
Double Blind Peer Reviewed.
https://jhrlmc.com/
DOI: https://doi.org/10.61919/jhrr.v4i3.1509
www.lmi.education/
LINK MEDICAL INTERFACE

Alveena Khan[1], Shima Algasim Abbas Alhindi[2], Aqsa Arbab Khan[2], Farhat Shireen[3], Surraya Halimi[4], Aysha Bibi[5]

Correspondence
Alveena Khan
alveena.khan71@gmail.com

Affiliations
1 Registrar, Obstetrics and Gynaecology, Letterkenny University Hospital, Ireland
2 Senior House Officer, Obstetrics and Gynaecology, Letterkenny University Hospital, Ireland
3 Senior Registrar, Obstetrics and Gynaecology, Letterkenny University Hospital, Ireland
4 Professor, Consultant Obstetrics and Gynaecology, Saidu Group of Teaching Hospital, Swat, Pakistan
5 Senior Registrar Obstetrics and Gynaecology, Saidu Group of Teaching Hospital, Swat, Pakistan

Keywords
Pre-eclampsia, Magnesium Sulfate, Severe Pre-eclampsia, Seizure Prophylaxis, Hypertensive Disorders

Disclaimers

Authors' Contributions	Conceptualization: Alveena khan and Surraya Haleemi Investigation and data collection: Alveena Khan, Data analysis: Alveena Khan, Shima Alhindi, Aqsa Khan, Farhat Shireen.
Conflict of Interest	None declared
Data/supplements	Available on request.
Funding	None
Ethical Approval	Respective Ethical Review Board
Study Registration	N/A
Acknowledgments	We are grateful to members in our group for assistance and discussion.

ABSTRACT

Background: Pre-eclampsia is a serious hypertensive disorder of pregnancy associated with significant maternal and neonatal morbidity and mortality. Magnesium sulfate ($MgSO_4$) is the standard treatment for seizure prevention in severe pre-eclampsia.

Objective: To compare the efficacy and safety of a single loading dose of $MgSO_4$ versus the standard regimen in patients with severe pre-eclampsia in Swat, Pakistan.

Methods: A randomized clinical trial was conducted on 248 pregnant women with severe pre-eclampsia at Saidu Group of Teaching Hospital, Swat. Participants were randomized into two groups: Group A received a single loading dose of 4 g intravenous $MgSO_4$ followed by 5 g intramuscularly, while Group B received the standard regimen of a loading dose followed by 1 g per hour intravenous infusion for 24 hours. Efficacy was assessed by the absence of seizure recurrence, and safety was evaluated based on complications like knee jerk reflex loss, low respiratory rate, and low urine output.

Results: Seizure recurrence occurred in 29.8% in Group A and 21.8% in Group B (p=0.147). Knee jerk reflex loss was significantly higher in Group A (48.4% vs. 24.2%; p=0.000), with no significant differences in low respiratory rate or urine output.

Conclusion: A single loading dose of $MgSO_4$ is as effective as the standard regimen for seizure prophylaxis in severe pre-eclampsia but is associated with higher knee jerk reflex loss.

INTRODUCTION

Pre-eclampsia is a complex multisystem disorder that arises during pregnancy, primarily characterized by the sudden onset of hypertension occurring after 20 weeks of gestation, often accompanied by proteinuria, uteroplacental dysfunction, or other maternal organ dysfunctions. It is one of the most severe complications of pregnancy, significantly contributing to maternal and perinatal morbidity and mortality worldwide. Each year, approximately 4 million women globally are diagnosed with pre-eclampsia, which leads to over 70,000 maternal deaths and approximately half a million fetal and neonatal deaths, highlighting the critical impact of this condition on maternal and neonatal health (1). Survivors of pre-eclampsia face long-term health challenges, including an increased risk of cardiovascular disease, diabetes, and stroke, as well as a shorter life expectancy (1, 2, 3). The condition also poses risks for the offspring, including prematurity, perinatal death, neurodevelopmental delays, and a heightened likelihood of developing cardiovascular and metabolic disorders later in life, which underscores the need for effective management strategies (1, 4).

The diagnostic criteria for pre-eclampsia have evolved over the past decade but generally include hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) on two occasions at least four hours apart, and proteinuria, or in the absence of proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms. These manifestations must develop after 20 weeks of gestation and resolve within six weeks postpartum. Pre-eclampsia can be further classified into early-onset, occurring before 34 weeks of gestation, and late-onset, occurring after 34 weeks, with each subtype exhibiting distinct clinical characteristics and etiologies. Early-onset pre-eclampsia is often associated with abnormal placentation and higher levels of antiangiogenic factors, whereas late-onset is more likely to be linked to maternal factors such as obesity and metabolic syndrome (5, 6, 7).

Management of pre-eclampsia focuses on controlling blood pressure and preventing seizures, with magnesium sulfate (MgSO4) being the gold-standard treatment for seizure prophylaxis in severe cases. MgSO4 is recognized by the World Health Organization as a high-priority and life-saving medication for severe pre-eclampsia and eclampsia due to its established efficacy in preventing and treating eclamptic seizures (8). The therapeutic action of MgSO4 involves the inhibition of neurotransmitter release and calcium entry in nerve cells, which stabilizes the neuronal membrane and

prevents seizure activity (9). Despite its efficacy, MgSO4 has a narrow therapeutic index and can cause dose-dependent toxicities, including respiratory depression and loss of deep tendon reflexes, particularly in settings with limited resources and monitoring capabilities (10, 11). This necessitates careful consideration of dosing strategies to balance efficacy and safety.

Various dosing regimens for MgSO4 have been explored to mitigate the risks of toxicity, including the use of lower doses or shorter treatment durations. These alternative regimens are particularly appealing in resource-limited settings where continuous monitoring is challenging. However, the literature on the comparative efficacy and safety of these regimens remains inconsistent, with variations reported based on patient demographics, geographic locations, and healthcare settings (12, 13). A loading dose of MgSO4, as opposed to the standard regimen involving a maintenance dose, could potentially offer similar efficacy in preventing seizures while minimizing adverse effects and resource use. This study aims to compare the efficacy and safety of a single loading dose of MgSO4 versus the standard regimen in patients with severe pre-eclampsia in Swat, Pakistan, a region with unique socioeconomic and healthcare challenges. By evaluating these dosing strategies in a randomized clinical trial, this research seeks to provide evidence for optimizing MgSO4 use in severe pre-eclampsia, particularly in settings with limited healthcare resources. The findings of this study could inform clinical practice guidelines and improve outcomes for women with severe pre-eclampsia in similar settings.

MATERIAL AND METHODS

The study was conducted as an open-label, parallel-group randomized controlled trial to compare the efficacy and safety of a loading dose of magnesium sulfate (MgSO4) versus the standard regimen in the management of severe pre-eclampsia in pregnant women. Ethical approval was obtained from the ethical review board of Saidu Teaching Hospital (STH), Swat, which serves as a major tertiary care and referral center for the surrounding districts and northern regions of Pakistan, conducting approximately 1,000 deliveries annually. The study was conducted in the Department of Obstetrics and Gynaecology, OBS-A Ward, STH. All procedures were carried out in accordance with the Declaration of Helsinki, ensuring ethical standards for research involving human participants.

The study population consisted of 248 pregnant women aged between 18 and 35 years, diagnosed with severe pre-eclampsia based on operational criteria, which included severe hypertension and other associated clinical manifestations. Participants were eligible for inclusion if they had a singleton pregnancy confirmed by ultrasound with a gestational age greater than 20 weeks. Exclusion criteria included known hypersensitivity to MgSO4, a history of myasthenia gravis, essential hypertension confirmed by clinical history or medical records indicating ongoing antihypertensive therapy, prior history of eclamptic fits treated outside the study setting, and refusal to participate in the study due to personal or social reasons.

Data collection was conducted over a period from November 2018 to June 2020. After obtaining written informed consent, participants were randomly assigned to one of two study groups using the lottery method: Group A received only a loading dose of MgSO4, while Group B received the standard dosing regimen as defined by the study's operational criteria. At the time of enrollment, baseline demographic and clinical data were collected from each participant through personal interviews and review of prenatal records. This included information on comorbidities, obstetric history, and details of the current pregnancy. Clinical data were systematically gathered from admission to discharge, including monitoring of vital signs and relevant biochemical parameters.

In Group A, participants received a loading dose of 4 g of 20% MgSO4 solution administered intravenously over 10-15 minutes, followed by 5 g administered intramuscularly into each buttock. Group B participants received the standard regimen, which involved the same initial loading dose followed by an intravenous infusion of 1 g per hour continued for 24 hours. Throughout the study, standard clinical management, including antihypertensive treatment, decisions on mode and timing of delivery, labor induction, and fetal monitoring, was provided in accordance with STH guidelines. Regular monitoring of blood pressure, patellar reflexes, respiratory rate, and urine output was conducted every three hours during MgSO4 administration. Continuous monitoring was maintained until blood pressure normalized after completion of MgSO4 therapy.

The primary outcome measure was the recurrence of seizures post-therapy, defined as convulsions occurring after the start of treatment in each group. Safety was assessed based on the occurrence of specific complications including loss of knee jerk reflex, defined as an absence of response upon patellar reflex testing; low respiratory rate, defined as a respiratory rate of fewer than 12 breaths per minute; and low urine output, defined as urine output of less than 100 mL in four hours post-treatment. All participant data were recorded on a customized proforma, with confidentiality maintained throughout the study.

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data, with means and standard deviations calculated for continuous variables such as age, gestational age, body mass index (BMI), parity, and blood pressure measurements. Frequencies and percentages were computed for categorical variables including socioeconomic status, residential status, seizure recurrence, and the occurrence of clinical complications such as knee-jerk reflex loss, low respiratory rate, and low urine output. Efficacy and safety comparisons between the two groups were made using the Chi-square test, with a p-value of ≤ 0.05 considered statistically significant. Stratification was performed to control for potential confounders including age, gestational age, parity, socioeconomic status, residential status, and BMI, with post-stratification analysis conducted using the Chi-square test.

This study aimed to determine whether a single loading dose of MgSO4 could provide a comparable efficacy and safety profile to the standard regimen in a resource-limited setting, potentially offering a viable alternative treatment strategy for severe pre-eclampsia in similar healthcare environments.

RESULTS

A total of 248 pregnant women diagnosed with severe pre-eclampsia, as defined by the operational criteria, were enrolled in the study. Participants were aged between 18 to 35 years, with a singleton pregnancy and gestational age over 20 weeks confirmed by ultrasound. The participants were randomly divided into two groups: Group A (n=124) received only the loading dose of MgSO4, and Group B (n=124) received the standard dosing regimen. The demographic characteristics, including maternal age, gestational age, BMI, parity, and blood pressure, were comparable between the two groups, indicating a balanced distribution of baseline variables. Seizure recurrence was observed in 25.8% of the total study patients. In Group A, seizure recurrence was noted in 29.8% of patients, while in Group B, it was observed in 21.8% of patients, with the difference being statistically insignificant (p-value=0.147).

Table 1: Demographic Characteristics of Participants

Variable	Group A (Loading Dose)	Group B (Standard Regimen)
Mean maternal age (years)	27.04 ± 4.50	26.81 ± 4.89
Mean gestational age (weeks)	29.36 ± 5.25	30.81 ± 5.48
Mean BMI (kg/m²)	27.70 ± 2.82	26.81 ± 2.79
Mean parity	1.75 ± 1.09	1.36 ± 1.01
Mean systolic blood pressure (mmHg)	169.35 ± 14.48	180.08 ± 15.82
Mean diastolic blood pressure (mmHg)	104.27 ± 11.63	103.31 ± 9.37

Table 2: Efficacy of Treatment in Both Groups by Seizure Recurrence

Efficacy (Seizure Recurrence)	Group A (Loading Dose)	Group B (Standard Regimen)	Total	p-value
Absent	37 (29.8%)	27 (21.8%)	64	0.147
Present	87 (70.2%)	97 (78.2%)	184	
Total	124 (100.0%)	124 (100.0%)	248	

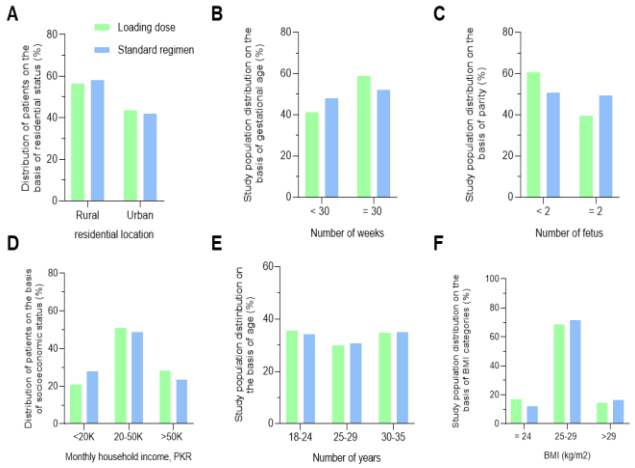

Figure 1: Distribution of patients for Loading dose vs standard regimen groups based on their residential location (A), Gestational age (B), parity (C), monthly income (D), age (E), and BMI (F).

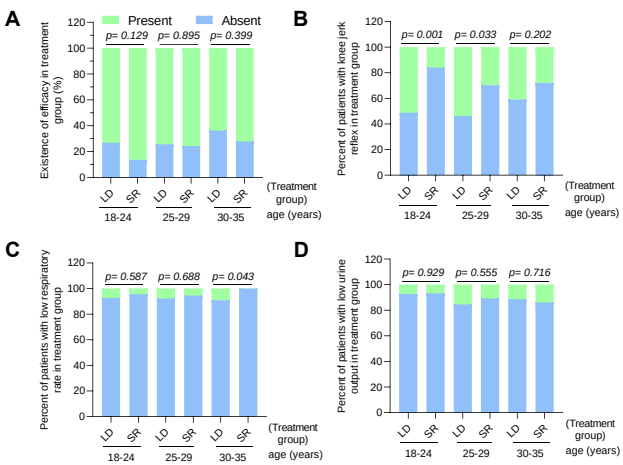

Figure 2: Existence of efficacy in treatment groups based on maternal age (A). Quantification for the percentage of patients experiencing clinical symptoms like KJR (B), LRR (C) LUO (D).

The safety analysis demonstrated no significant differences between the two groups regarding the incidence of low respiratory rate (p-value=0.099) and low urine output (p-value=0.838). However, a statistically significant difference was noted in the knee jerk reflex, with 51.6% absence in Group A compared to 75.8% in Group B (p-value=0.000), indicating a higher occurrence of this complication in the loading dose group. Most participants were from rural areas and belonged to the middle-class socioeconomic status (income between 20,000 to 50,000 PKR per month). Further stratification by demographic factors such as maternal age, gestational age, parity, and BMI showed balanced distributions with no significant differences influencing the study outcomes. The stratification analysis by maternal age, gestational age, BMI, parity, socioeconomic status, and residential status revealed no statistically significant differences in treatment efficacy between the groups. However, knee jerk reflex differences were significant across most effect modifiers, including maternal age, gestational age, BMI, parity, and socioeconomic and residential status, while low respiratory rate and low urine output showed no

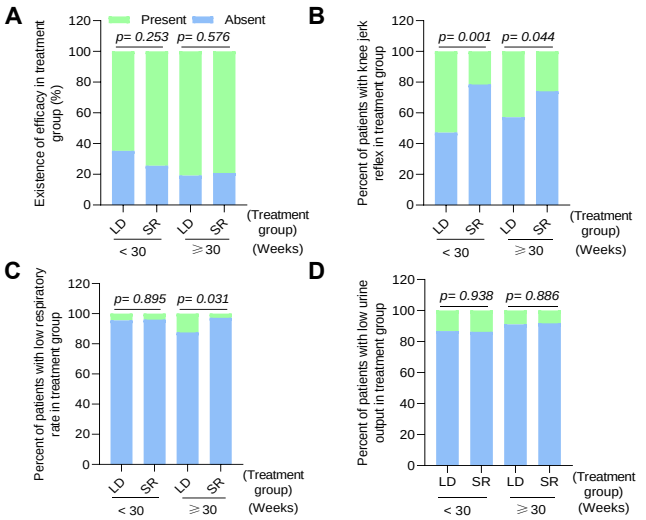

Figure 3: Existence of efficacy in treatment groups based on gestational age (A). Quantification for the percentage of patients experiencing clinical symptoms like KJR (B), LRR (C) LUO (D).

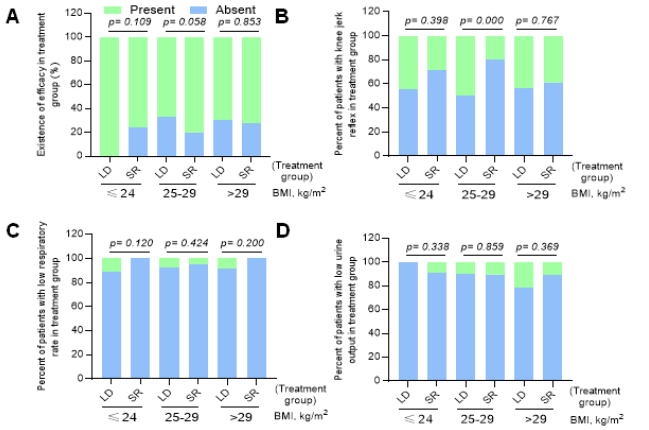

Figure 4: Existence of efficacy in treatment groups based on gestational age (A). Quantification for the percentage of patients experiencing clinical symptoms like KJR (B), LRR (C) LUO (D).

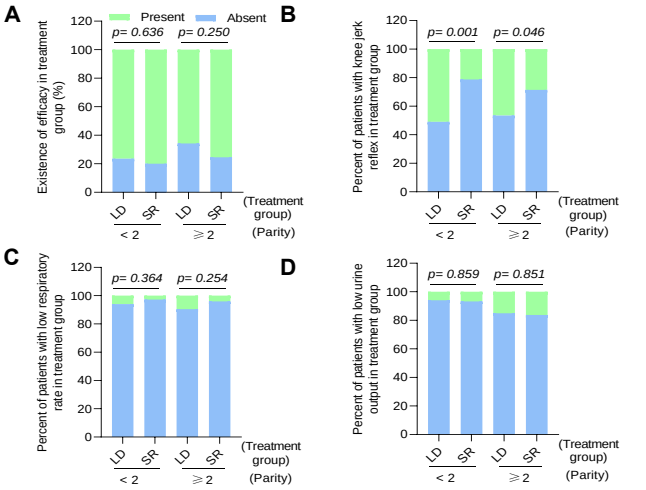

Figure 5: Existence of efficacy in treatment groups based on gestational age (A). Quantification for the percentage of patients experiencing clinical symptoms like KJR (B), LRR (C) LUO (D).

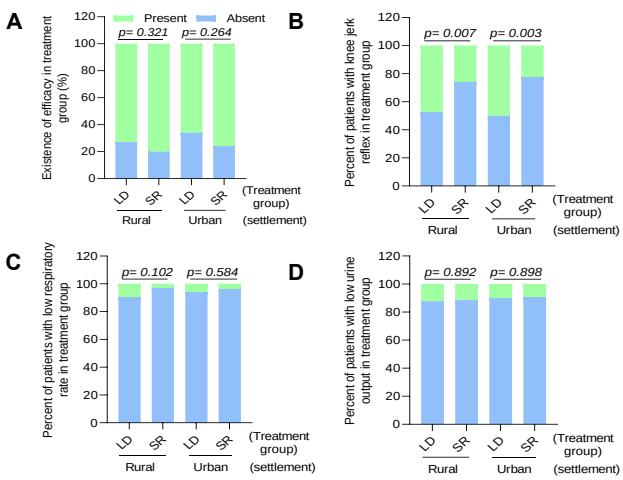

Figure 6: Existence of efficacy in treatment groups based on settlement (A). Quantification for the percentage of patients experiencing clinical symptoms lie KJR (B), LRR (C) LUO (D).

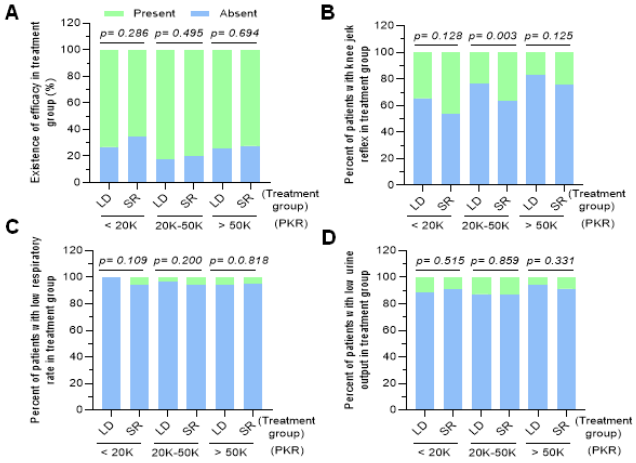

Figure 7: Existence of efficacy in treatment groups based on financial income status (A). Quantification for the percentage of patients experiencing clinical symptoms like KJR (B), LRR (C) LUO (D).

notable associations with any effect modifiers. Overall, the study demonstrated that a single loading dose of MgSO4 is as effective as the standard dose regimen for seizure prophylaxis in severe pre- In these figures, the heights of the bars vary, showing the differences between the two groups in each category. For some categories, one group consistently has higher values, while in others, the differences are less pronounced or reversed. This pattern suggests variability in performance or measurements across the conditions being compared.

The subsequent sets of figures depict stacked bar charts, where each bar is divided into segments corresponding to the two groups, allowing for a visual comparison of proportions within each category. The stacked bars make it easier to assess the combined total and relative contributions of each group in a given category. In these figures, variations in the height and composition of the bars

highlight shifts in the balance between the two groups across different conditions.

Throughout these comparisons, a common theme is the fluctuating dominance between the groups, with some conditions favoring one group and others showing more balanced or opposite results. These visualizations collectively provide a comprehensive overview of group performance or characteristics across multiple dimensions, emphasizing the importance of context in interpreting comparative data. eclampsia. Both regimens are equally safe concerning the incidence of low respiratory rate and low urine output, although the standard regimen is associated with a lower incidence of knee jerk reflex absence.

The figures you provided represent various bar charts comparing two groups across multiple conditions or time points. The first set of figures (from the initial images) illustrates basic side-by-side bar comparisons, where each pair of bars represents the values of two groups (indicated by different colors, such as green and blue) across different categories or time intervals.

Table 3: Complications of Treatment in Both Groups

Complication	Proportion	Group A (Loading Dose)	Group B (Standard Regimen)	Total	p-value
Knee Jerk Reflex (Absent)	Present	60 (48.4%)	30 (24.2%)	90	0.000
	Absent	64 (51.6%)	94 (75.8%)	158	
	Total	124 (100.0%)	124 (100.0%)	248	
Low Respiratory Rate	Present	10 (8.1%)	4 (3.2%)	14	0.099
	Absent	114 (91.9%)	120 (96.8%)	234	
	Total	124 (100.0%)	124 (100.0%)	248	
Low Urinary Output	Present	14 (11.3%)	13 (10.5%)	27	0.838
	Absent	110 (88.7%)	111 (89.5%)	221	
	Total	124 (100.0%)	124 (100.0%)	248	

DISCUSSION

The findings of this study indicate that a single loading dose of MgSO4 is as effective as the standard dosing regimen for seizure prophylaxis in patients with severe pre-eclampsia. The recurrence of seizures did not differ significantly between the two groups, which aligns with previous studies that have evaluated the efficacy of varying MgSO4 regimens in managing severe pre-eclampsia (21). This outcome is consistent with the results from similar settings where MgSO4 was used to prevent eclamptic seizures, demonstrating that even reduced or alternative dosing regimens can be effective, particularly in resource-limited environments (22).

The analysis showed no significant differences between the groups in terms of respiratory complications or urinary output, suggesting that both regimens are equally safe concerning these outcomes. However, the absence of knee jerk reflex was significantly more common in the group that received the loading dose alone, which could be attributed to variations in serum magnesium levels due to the lack of maintenance doses. This complication has been noted in other studies and reflects the importance of careful monitoring when deviating from standard protocols (23). Although MgSO4 is widely recognized for its effectiveness in preventing eclamptic seizures, its administration requires meticulous monitoring to avoid dose-dependent toxicities such as respiratory depression and loss of reflexes (15). The balance between efficacy and safety is critical, particularly in settings where patient monitoring capabilities may be limited.

The study's strengths include its randomized controlled design, which minimizes bias and provides robust evidence for comparing the efficacy and safety of different MgSO4 regimens. Additionally, the study's setting in a major referral center in Swat allows the findings to be relevant to similar low-resource settings where severe pre-eclampsia remains a significant contributor to maternal morbidity and mortality. This study is one of the first to explore a simplified regimen of MgSO4 in a Pakistani cohort, adding valuable data to the global body of evidence supporting alternative dosing strategies (21, 22).

However, the study also had limitations, including the relatively short duration of follow-up, which may have missed late-onset complications or recurrent seizures beyond the immediate postpartum period. Additionally, the sample size, while adequate for detecting differences in seizure recurrence, may have been underpowered to fully assess differences in rarer complications or outcomes such as maternal or neonatal mortality. The study also relied on clinical monitoring without serum magnesium level measurements, which could have provided a more detailed understanding of the relationship between dosing and toxicity (13). Moreover, the findings are most applicable to settings with similar demographic and clinical profiles and may not generalize to populations with different health care capabilities or baseline characteristics.

Future studies should aim to include a larger sample size and longer follow-up period to capture more comprehensive data on the safety and efficacy of alternative MgSO4 regimens. It would also be beneficial to include biochemical monitoring to better correlate clinical outcomes with magnesium levels, allowing for more precise adjustments in dosing. Research in other regions and settings would help to determine the broader applicability of the findings and support the development of context-specific guidelines for managing severe pre-eclampsia.

Overall, the study contributes to the growing evidence that a loading dose of MgSO4 can be a viable alternative to the standard regimen, offering a potentially more feasible option in resource-limited settings. The comparable efficacy in preventing seizures, coupled with the safety profile observed, suggests that simplified dosing regimens could alleviate some of the logistical and economic burdens associated with the standard MgSO4 therapy, provided that appropriate monitoring protocols are in place. These findings support the continued exploration and validation of alternative MgSO4 regimens to improve the management of severe pre-eclampsia and reduce the associated maternal and neonatal morbidity and mortality (15, 16).

CONCLUSION

The study concluded that a single loading dose of magnesium sulfate ($MgSO_4$) is as effective as the standard regimen in preventing seizure recurrence in patients with severe pre-eclampsia. Both treatment approaches demonstrated comparable safety profiles concerning the incidence of low respiratory rate and low urine output, highlighting their utility in clinical settings, especially where resources for continuous monitoring are limited. However, the significantly higher occurrence of knee jerk reflex loss in the loading dose group suggests the need for cautious evaluation when opting for this regimen, as it may pose additional neuromuscular risks. These findings emphasize the potential of a simplified $MgSO_4$ regimen in resource-limited settings, though further studies are recommended to confirm these results and explore optimal dosing strategies that minimize side effects. Future research should also consider larger, multicenter trials to enhance the generalizability of these findings and explore the long-term outcomes of both regimens on maternal and neonatal health. The adaptation of $MgSO_4$ dosing strategies should balance efficacy with safety, taking into account individual patient profiles and healthcare settings to optimize maternal and neonatal outcomes in severe pre-eclampsia management.

REFERENCES

1. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Pre-Eclampsia: A Pragmatic Guide for First-Trimester Screening and Prevention. Int J Gynecol Obstet. 2019;145(Suppl 1):1-33. doi: 10.1002/ijgo.12802.
2. Kvalvik LG, Wilcox AJ, Skjærven R, Østbye T, Harmon QE. Term Complications and Subsequent Risk of Preterm Birth: Registry-Based Study. BMJ. 2020;369. doi: 10.1136/bmj.m1007.
3. Pittara T, Vyrides A, Lamnisos D, Giannakou K. Pre-Eclampsia and Long-Term Health Outcomes for Mother and Infant: An Umbrella Review. BJOG. 2021;128(9):1471-83. doi: 10.1111/1471-0528.16683.
4. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, et al. Cardiovascular Risk Factors in Children and Young Adults Born to Preeclamptic Pregnancies: A Systematic Review. Pediatrics. 2012;129(6). doi: 10.1542/peds.2011-3093.
5. Ness RB, Roberts JM. Heterogeneous Causes Constituting the Single Syndrome of Preeclampsia: A Hypothesis and Its Implications. Am J Obstet Gynecol. 1996;175(5):1365-70. doi: 10.1016/S0002-9378(96)70056-X.
6. Von Dadelszen P, Magee LA, Roberts JM. Subclassification of Preeclampsia. Hypertens Pregnancy. 2003;22(2):143-8. doi: 10.1081/PRG-120021060.
7. Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Risk Factors for Preeclampsia in Nulliparous Women in Distinct Ethnic Groups: A Prospective Cohort Study. Obstet Gynecol. 1998;92(2):174-8. doi: 10.1016/S0029-7844(98)00143-4.
8. Masuyama H, Nobumoto E, Kyozuka H, Komiyama H, Shimokawa M, Kaneko H, et al. Different Profiles of Circulating Angiogenic Factors and Adipocytokines Between Early- and Late-Onset Pre-Eclampsia. BJOG. 2010;117(3):314-20. doi: 10.1111/j.1471-0528.2009.02453.x.
9. Chaemsaithong P, Sahota DS, Poon LC. First Trimester Preeclampsia Screening and Prediction. Am J Obstet Gynecol. 2022;226(2). doi: 10.1016/j.ajog.2020.07.020.
10. Papageorghiou AT, Yu CKH, Cicero S, Bower S, Nicolaides KH. Second-Trimester Uterine Artery Doppler Screening in Unselected Populations: A Review. J Matern Fetal Neonatal Med. 2002;12(2):78-88. doi: 10.1080/JMF.12.2.78.88.
11. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH. Multicenter Screening for Pre-Eclampsia and Fetal Growth Restriction by Transvaginal Uterine Artery Doppler at 23 Weeks of Gestation. Ultrasound Obstet Gynecol. 2001;18(5):441-9. doi: 10.1046/j.0960-7692.2001.00572.x.
12. Aardema MW, Oosterhof H, Timmer A, Van Rooy I, Aarnoudse JG. Uterine Artery Doppler Flow and Uteroplacental Vascular Pathology in Normal Pregnancies and Pregnancies Complicated by Pre-Eclampsia and Small for Gestational Age Fetuses. Placenta. 2001;22(5):405-11. doi: 10.1053/plac.2001.0676.
13. Voigt HJ, Becker V. Doppler Flow Measurements and Histomorphology of the Placental Bed in Uteroplacental Insufficiency. J Perinat Med. 1992;20(2):139-45. doi: 10.1515/jpme.1992.20.2.139.
14. Espinoza J, Chaiworapongsa T, Romero R, Kim YM, Kim MR, Yoshimatsu J, et al. Normal and Abnormal Transformation of the Spiral Arteries During Pregnancy. J Perinat Med. 2006;34(6):447-58. doi: 10.1515/JPM.2006.089.
15. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium Sulphate and Other Anticonvulsants for Women with Pre-Eclampsia. Cochrane Database Syst Rev. 2010;(11). doi: 10.1002/14651858.CD000025.pub2.
16. Simon J, Gray A, Duley L. Cost-Effectiveness of Prophylactic Magnesium Sulphate for 9996 Women

with Pre-Eclampsia from 33 Countries: Economic Evaluation of the Magpie Trial. BJOG. 2006;113(2):144-51. doi: 10.1111/j.1471-0528.2005.00785.x.
17. Duley L. Maternal Mortality Associated with Hypertensive Disorders of Pregnancy in Africa, Asia, Latin America and the Caribbean. BJOG. 1992;99(7):547-53. doi: 10.1111/j.1471-0528.1992.tb13818.x.
18. 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. doi: 10.1016/S0140-6736(06)68397-9.
19. Arulkumaran N, Lightstone L. Severe Pre-Eclampsia and Hypertensive Crises. Best Pract Res Clin Obstet Gynaecol. 2013;27(6):877-84. doi: 10.1016/j.bpobgyn.2013.07.003.
20. Bigdeli M, Zafar S, Assad H, Ghaffar A. Health System Barriers to Access and Use of Magnesium Sulfate for Women with Severe Pre-Eclampsia and Eclampsia in Pakistan: Evidence for Policy and Practice. PLoS One. 2013;8(3). doi: 10.1371/journal.pone.0059158.
21. Rimal SP, Rijal P, Bhatt R, Thapa K. Loading Dose Only Versus Standard Dose Magnesium Sulfate Seizure Prophylaxis in Severe Pre-Eclamptic Women. J Nepal Med Assoc. 2017;56(208):343-7. doi: 10.31729/jnma.3431.
22. Shoaib T, Khan S, Javed I, Bhutta SZ. Loading Dose of Magnesium Sulphate Versus Standard Regime for Prophylaxis of Pre-Eclampsia. J Coll Physicians Surg Pak. 2009;19(1):30-3. doi: 01.2009/JCPSP.3033.
23. Dasgupta S, Saha SK, Bhowal J, Ganguly R. Single Loading Dose of Magnesium Sulphate in Severe Preeclampsia and Eclampsia-Is It Effective? A Randomized Prospective Study. Obstet Gynecol Int J. 2015;2(6):00059. doi: 10.15406/ogij.2015.02.00059.
24. Sharma A, Gupta K, Nigam A, Pathania K. Comparison of Low Dose Dhaka Regimen of Magnesium Sulphate with Standard Pritchard Regimen in Eclampsia. Int J Reprod Contracept Obstet Gynecol. 2016;5(9):3044-9. doi: 10.18203/2320-1770.ijrcog20163870.
25. Kanti V, Bhowmik S, Ganguli D, Ghosh D. Comparison Between Intramuscular and Intravenous Regimen of Magnesium Sulfate in Management of Severe Pre-Eclampsia and Eclampsia. Int J Reprod Contracept Obstet Gynecol. 2015;4(1):1-6. doi: 10.5455/2320-1770.ijrcog20150235.