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# Comparison Of Loading Dose Magnesium Sulphate With Pritchard Regimen In The Management Of Severe Preeclamsia And Eclampsia In A Resource Poor Setting, Southeast Nigeria.

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***ABSTRACT***
***Background:*** *Preeclampsia/eclampsia is part of a spectrum of multi-systemic pregnancy disorder that contributes substantially to maternal and perinatal morbidity and mortality, especially in low resource setting. This study was done in Abakaliki, Ebonyi State, Southeast Nigeria.*
***Objectives:*** *To compare the efficacy of loading dose of magnesium sulphate with that of the Pritchard regimen in the prevention of eclampsia in patients with severe preeclampsia and recurrent fits in eclampsia in a low resource setting like ours.*
***Methods:*** *This was a prospective, single blinded randomized controlled study of loading dose versus Pritchard regimens of MgSO4 at a Teaching Hospital Abakaliki. One hundred and twenty patients were recruited 60 to each arm using computer-generated numbers. Social demographic characteristics, efficacy and adverse effects of the drug on the mother and baby were noted. Data were collated, tabulated and analyzed using the statistical package for social sciences (SPSS) software (version 22, Chicago II, USA)*
***Results:*** *The efficacy of MgSO4 in prevention of fits was similar in both arms of the study. There was a statistically significant difference in the side-effect of MgSO4 with larger participants in group B (Pritchard regimen) complaining of pain and hot flushes compared to group A (loading dose), prticipants $p < 0.001$.*
***Conclusion:*** *The loading dose of MgSO4 is as effective as the standard Pritchard regimen in controlling seizures in both severe pre-eclampsia and eclampsia, and has an added advantage of reduced side-effect.*
***Keywords:*** *Eclampsia, pre-eclampsia, poor resource setting.*

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## I. INTRODUCTION

Preeclampsia/eclampsia is part of a spectrum of life-threatening multisystem pregnancy disorder affecting about 2-8% of all pregnancies worldwide[1]. It has a substantial impact on maternal and perinatal morbidity and mortality especially in resource poor settings[2]. About 50000 women die each year globally from it[3]. Pre-eclampsia is a disorder of widespread vascular endothelial dysfunction occurring after 20 weeks gestation, characterized by hypertension and proteinuria, in a previously normotensive non proteinuric patient and resolves within six weeks postpartum. It may become complicated with eclampsia, which is the occurrence of generalized tonic-clonic seizures in a woman with preeclampsia that cannot be attributed to other causes of convulsion[4]. It accounts for12 to 25 % fetal growth restriction and small for gestational age as well as 15 to 20 % of all preterm births[5]. Eclampsia accounts for a significant number of maternal deaths in Africa, Asia and the Carribean[6.] In Northern Nigeria, the incidence of preeclampsia was 9.42% in Birnin kudu and 1.02% in Kano[6]. In Abakaliki, Ebonyi state in South East Nigeria the prevalence of preeclampsia is 0.99% while that of eclampsia is 0.76%[7].

The management of severe preeclampsia and eclampsia is based on careful assessment, stabilization, continued monitoring and delivery at the optimal time for the mother and her baby. This involves control of blood pressure and prevention of convulsions in patients with severe preeclampsia and recurrence of fits in patients with

eclampsia in addition to other resuscitative efforts such as maintenance of airway, ensuring patient is breathing and ensuring adequate circulation[8].

Magnesium sulphate is the drug of choice in prevention of seizures in patients with severe preeclampsia and recurrence of seizures in patients with eclampsia. It has been shown to be more effective and with fewer side effects than previously used drugs such as diazepam and phenytoin. In 1995 the Eclampsia Trial collaborative group reported a reduction in the risk of recurrence of seizures by 52% in women with eclampsia compared with diazepam and by 67% compared with phenytoin[9]. The Magpie Trial reported that severe preeclamptic women treated with magnesium sulphate had a 58% lower risk of developing eclampsia and the use of Magnesium sulphate in patients with severe pre-eclampsia reduced the risk of progression to eclampsia by more than half and also reduced maternal mortality[10].

Magnesium sulphate has been in use in the management of preeclampsia and eclampsia but its mechanism of action remains unclear. It is thought to act both as a peripheral and cerebral vasodilator, reduce cerebral edema and protect the blood brain barrier. It blocks calcium inflow by inhibiting N-methyl D- Aspartate receptors in the brain and also produce peripheral arteriolar dilatation which reduces the blood pressure[11]. Following administration about 40% is bound to protein while the unbound component diffuses into the extravascular space, bone, across the placenta and into the fetal membranes and the fetus. Magnesium sulphate is excreted almost exclusively in the urine with 90% of the dose excreted in the first 24hours. Following intravenous administration there is a rapid distribution phase followed by a slow distribution phase. The first warning of impending toxicity in the mother is loss of patellar reflex at plasma concentration of 3.5 to 5mmol/L. respiratory paralysis occurs at 5 to 6.5mmol/L while cardiac conduction is altered at 12.5mmol/L[12].

A potential concern for magnesium sulphate therapy is the risk of side effects which could increase with the duration of treatment especially if there are challenges in clinical monitoring of the patients. These side effects include a feeling of warmth, flushing, nausea and vomiting, muscle weakness, somnolence, dizziness, pain and irritation at the injection site. More serious side effects are rare but include the loss of the patellar reflex, respiratory depression and cardiac arrest[13]. As a result of these side effects, different durations of administration had been tried with different results. These have led to trials comparing alternative treatment regimens which are too small for reliable conclusions[5]. Various regimens with different duration of treatment have been used over the years but there are still questions with regard to the minimum effective dose of magnesium sulphate therapy[14.] Regimens that have been used include Pritchard, Zuspan, Sibai and several low dose and loading dose only regimens[15]. The Pritchard Regimen has been the gold standard for the prevention of eclampsia. It is the most popular and time tested[16.] However, several other alternative regimens have been proposed and used all aimed at minimal side effects.

The routine administration of maintenance doses of magnesium sulphate to patients after an initial loading dose has been at best empirical[17]. It has not been subjected to large scale trials. Although several studies have compared the Pritchard and loading dose regimen there are conflicting results of efficacy between the two regimens. This study is aimed at determining the efficacy of loading dose only magnesium sulphate regimen in preventing eclampsia or recurrence of seizures. This study is apt in our low- resource setting where equipment and manpower for monitoring the preeclamptic and eclamptic patients and for institution of maintenance doses of magnesium sulphate may be unavailable or unaffordable. Again, if loading dose magnesium sulphate is found to be of comparable efficacy with the standard Pritchard Regimen it will save the patients from the side effects of the drug, reduce cost and free medical manpower to attend to urgent needs of other patients. A loading dose only regimen will be important in patients in whom the maintenance dose is contraindicated. It is against this background and coupled with the fact that no such study had been carried out in our practice environment that necessitated this study.

## II. MATERIALS AND METHODS

This was a single blinded non-inferiority randomized controlled trial conducted in the Hospital, Abakaliki in Ebonyi state, Nigeria within a period of six months. The state was created on October 1, 1996, has 13 local government areas with Abakaliki the only urban settlement, Afikpo semi-urban, the rest rural. Majority of the people are subsistent farmers, poor and with poor maternal health indices.

All pregnant women with diagnosis of severe preeclampsia or eclampsia admitted through the antenatal clinic, labor ward or obstetric emergency unit that met the inclusion criteria and consented were included in the study. Exclusion criteria includes refusal of consent, pre-viable pregnancy, received magnesium sulphate, mild preeclampsia, chronic hypertension and other Medical or Obstetric complication of pregnancy.

**SAMPLE SIZE DETERMINATION**

The minimum sample size was determined using statistical formula for non-inferiority study design.

$$N = \frac{2\times[Z_{1-\alpha/2}+Z_{1-\beta}]^2 \times P \times (1-P)}{d_o}$$

where
N = number per group
Z = the standard normal deviate usually set at 1.96.
$d_0$ = acceptable margin of equivalence set at 0.05
P = proportion of patients from a previous related study (0.2)
α = type I error = ≤5%
β = type II error =≤ 20%

$$N = 2 \times \frac{(1.96+0.845)^2}{0.05} \times 0.2(1-0.2)$$

$$N = \frac{2 \times 7.868 \times 0.2 \times 0.8}{0.05}$$

$$N = \frac{2.517768}{0.05}$$

$N = 50.36 \approx 50$

Giving a 10% attrition rate, the total number of cases per arm was 50+6=56 and a total of 112 cases for both arms

All patients selected for the study were randomized into Group A, loading dose only regimen and group B, standard Pritchard regimen using computer generated random numbers. They were monitored for seizures, side effects, toxicity and neonatal outcomes. Patients that developed complication was immediately managed according to departmental protocol.

Magnesium sulphate used for this study was of the brand Magphate® which comes in 5g of 50% in 10ml of water. This was procured from Zolon Health Care limited, Lagos; a standard pharmaceutical company approved by the National Agency for Food and Drug Administration and Control (NAFDAC). All the ampoules were of the same batch number, manufacturing and expiry dates. This ensured that all the participants in this research received the same drug quality. The drug had a shelf life of 24months and was stored at room temperature. Participants, who met the inclusion criteria, having signed the informed consent form, were given sequential study numbers and the corresponding numbered opaque sealed envelope were then allocated to the patient. These numbers (1-120) were inscribed on brown envelopes and a piece of paper with the respective drug inside these envelopes and sealed.

Group A: received loading dose as 4g of 20% $MgSO_4$ (Magphate®) I.V. over 10 minutes, followed by 5g of 50% $MgSO_4$ I.M. in each buttock. There were no maintenance doses. (loading dose only regimen).

Group B: received 4g of 20% intravenous (I.V.) $MgSO_4$ (Magphate®, Zolon Health Care Ltd) given over 10 minutes, followed by 5g of 50% intramuscular (I.M.) $MgSO_4$ in each buttock statim using a 22G needle. Then, maintenance doses were given as 5g of 50% $MgSO_4$ administered intramuscularly in alternate buttocks 4 hourly for 24 hours, for patients with severe preeclampsia and for 24 hours post-delivery or post last seizure episode, whichever occurred last, for patients with eclampsia.

Patients were monitored clinically for signs of toxicity by counting the respiratory rate a minute hourly. The rate 16 or more was normal. Deep tendon reflex was checked hourly and all documented in monitoring chart. Hourly urine output with catheter was measured hourly. Output of ≥ 30ml/hour was normal. Before administration of the next dose of magnesium sulphate all these parameters were checked and found normal. One gram of calcium gluconate was provided for each patient to be given if toxicity occurs. A questionnaire on possible side effects of magnesium sulphate was administered on each patient after the last dose of the injection on the Pritchard regimen to determine the side effect profile on the two arms of the study. Questions asked included a feeling of warmth, nausea, vomiting, weakness of the body, somnolence, dizziness, etc. Also, the Apgar score of each baby delivered was taken at 1 and 5 minutes respectively. Patients' vital signs were checked before $MgSO_4$ administration. Data were collated and the coded data fed into the computer using the statistical package for social sciences (SPSS) software (version 22, Chicago USA) and analysis done. A p-value <0.05 was considered significant.

**ETHICAL ISSUES**

Ethical approval was obtained from the Health Research and Ethics Committee of the Hospital. Each participant signed informed consent form. But for unconscious patient, consent was obtained from the spouse or the nearest relative. The participants were made to understand that declining participation would have no adverse consequences in her obtaining adequate care and can opt out at any time if they do not wish to continue. All the information was kept confidential and was used only for the study, the drugs were free for the participants and all the cost of investigations were born by the researchers.

## III. RESULTS

One hundred and twenty (120) women participated in the study 60 in each group A and B.

**Table 1;** Sociodemographic/Obstetrics characteristics of the participants

| **Variable n, (%)** | **Group A n, (%)** | **Group B** | **$X^2$** | **p – value** |
|---|---|---|---|---|
| Maternal age (years) | | | | |
| < 20 | 5(8.3) | 2(3.3) | 1.374 | 0.503 |
| 20-34 | 11(18.3) | 12(20.0) | | |
| ≥ 35 | 44(73.3) | 46(76.7) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Marital status | | | | |
| Married | 53(88.3) | 55(91.7) | 0.370 | 0.543 |
| Single | 7(11.7) | 5(8.3) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Booking status | | | | |
| Booked | 50(83.3) | 49(81.7) | 0.058 | 0.810 |
| Unbooked | 10(16.7) | 11(18.3) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Parity | | | | |
| 1 | 38(63.3) | 34(56.7) | 1.567 | 0.457 |
| 2-4 | 14(23.3) | 20(33.3) | | |
| ≥ 5 | 8(13.4) | 6(10.0) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Educational level | | | | |
| Primary | 4(6.7) | 7(11.7) | 1.067 | 0.586 |
| Secondary | 38(63.3) | 34(56.7) | | |
| Tertiary | 18(30.0) | 19(31.6) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Admission Status | | | | |
| Pre-eclampsia | 53(88.3) | 49(81.7) | 1.046 | 0.306 |
| Eclampsia | 7(11.7) | 11(18.3) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Delivery route | | | | |
| SVD | 39(65.0) | 32(53.3) | 1.690 | 0.194 |
| C/S | 21(35.0) | 28(46.7) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |

SVD = Spontaneous Vaginal Delivery
C/S = Caesarean section
Table 1. No significant difference in any of the sociodemographic/obstetric characteristics.

**Table 2:** Comparison of effectiveness of the two study groups

| **Variable n, (%)** | **Group A n, (%)** | **Group B** | **$X^2$** | **p – value** |
|---|---|---|---|---|
| **Fit Occurrence (severe preeclamptics)** | | | | |
| Yes | 5(9.4) | 2(4.1) | 1.141 | 0.439 |
| No | 48(90.6) | 47(95.9) | | |
| **Total** | **53(100.0)** | **49(100.0)** | | |
| **Fit Recurrence (eclamptics)** | | | | |
| Yes | 2(28.6) | 2(18.2) | 0.267 | 0.605 |
| No | 5(71.4) | 9(81.8) | | |
| **Total** | **7(100.0)** | **11(100.0)** | | |

No difference in terms of occurrence of fit. Table 2.

**Table 3;** Maternal side effect/complications

| **Variable n, (%)** | **Group A n, (%)** | **Group B** | **X $^2$** | **p – value** |
|---|---|---|---|---|
| **Side effects** | | | | |
| Pain/Hot flushes | 7(11.7) | 29(48.3) | 19.206 | < 0.001* |
| No side effect | 53(88.3) | 31(51.7) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |

*=> Statistically significant

There was significant difference among the groups in terms of side effects Table 3.

**Table 4;** Comparison of neonatal death and admission

| **Variable n, (%)** | **Group A n, (%)** | **Group B** | **X $^2$** | **p – value** |
|---|---|---|---|---|
| NICU Admission | | | | |
| Yes | 8(13.3) | 7(11.7) | 0.076 | 0.783 |
| No | 52(86.7) | 53(88.3) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |
| Neonatal death | | | | |
| Yes | 1(1.7) | 3(5.0) | 1.034 | 0.309 |
| No | 59(98.3) | 57(95.0) | | |
| **Total** | **60(100.0)** | **60(100.0)** | | |

NICU – Newborn Intensive Care Unit

**Table 5** comparison of APGA score and birth weight

| **Variable Mean±SD** | **Group A Mean±SD** | **Group B** | **95%CI** | **p – value** |
|---|---|---|---|---|
| Birth weight(skg) | 3.11± 0.59 | 3.03 ± 0.59 | - 0.398 to 0.284 | 0.501 |
| APGAR 1st min | 7.73 ± 1.98 | 7.87 ± 2.51 | - 0.950 to 0.682 | 0.747 |
| APGAR 5th min | 9.18 ± 1.64 | 8.88 ± 2.37 | - 0.438 to 1.038 | 0.422 |

No difference in neonatal outcomes between the two arms table 4 and 5.

## IV. DISCUSSION

The sociodemographic and obstetric characteristics of the two arms of the study on admission and delivery route were similar. It showed that unbiased randomization and as such, the findings would be a good representation of the population and could be generalized. Majority of cases, making up 38(63.3%) and 34(56.7%) of groups A and B respectively were primigravidae. This was similar to previous reports[8,14,18]. It was reported commoner in primigravida[4]. The routes of delivery were comparable in both arms. This was similar to previous findings[18]. These studies had similar methodology. Significant difference in the route of delivery was recorded in Pakistan[19]. This may due to their smaller sample size.

These were no statistically significant in the two arms in terms of occurrence or recurrence of seizures. This were similar to the findings in Nepal[6,18]. Complaints of pain and hot flushes were recorded more in group B compared to group A and this was statistically significant ($p < 0.001$). Similar findings were noted in previous studies[8,14,18,20]. No major toxicity was noted and no maternal mortality was recorded in this study.

The neonatal outcomes of all the parameters checked were similar in both arms. These were similar to previous reports[8,13]. Four neonatal deaths were recorded in this study due to prematurity and all occurred in the Newborn Intensive Care Unit.

The weakness, lacuna and limitation of this study are, small sample size, hospital based, hence may not be a true representation of the population who are mostly rural dwellers and may not have access to the hospital.

## V. CONCLUSION

The loading dose of MgSO4 is as effective as the standard Pritchard regimen in controlling seizures in both severe pre-eclampsia and eclampsia, and has an added advantage of reduced side-effect.

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**CONFLICT OF INTEREST**

None declared.

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