# THE RELATIONSHIP BETWEEN SERUM MAGNESIUM LEVELS AND THE OCCURRENCE OF CONVULSIONS IN WOMEN TREATED WITH MAGNESIUM SULPHATE FOR SEVERE PREECLAMPSIA AND ECLAMPSIA.


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## DECLARATION

I declare that this research in part fulfillment of the M.Med degree in Obstetrics and Gynecology is my original work and has not been presented for a degree award in any other University.

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## DEDICATION

Dedicated to my parents Joseph Machira and Mary Wangari who lovingly supported me as I did this work.

## ACKNOWLEDGEMENTS

I am greatly indebted to Professor Ndavi and Dr. Magoha for patiently studying my work time and time again and offering their guidance and suggestions. I would also like to thank Professor Kigondu and Dr. Kiarie for reviewing my study.

I also would like to thank the following people for being of great assistance during the study:

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⇒ The matron and all the midwives in the maternity wards of KNH and PMH for being very cooperative and assisting in data collection.

## DEFINITIONS

1. Eclampsia: New-onset grand mal seizures in a woman during pregnancy or postpartum with preeclampsia with at least two of the following features recorded within 24 hours of the convulsion, Hypertension ( a diastolic pressure of at least 90 mm Hg) , Proteinuria (at least 2+ proteins in a random urine sample)that cannot be attributed to other causes .

2. Preeclampsia: A multi system disorder of unknown etiology characterized by development of hypertension (140/90 on at least 2 occasions 6 hours apart) or proteinuria usually after 20 weeks in a previously normotensive patient.

3. Severe Pre-eclampsia :Patient with pre-eclampsia with persistent systolic blood pressure of $\geq$160/100 mm Hg or persistent severe epigastric pains, cerebral or visual disturbances, oliguria, proteinuria more than or equal to 5 grams per 24 hours, thrombocytopenia $\leq$ 100,000/$mm^3$, HELLP syndrome, IUGR or pulmonary oedema.

4. Gestational hypertension – Any form of new-onset pregnancy related hypertension.

5. Chronic hypertension – A BP of more than 140/90 before pregnancy or diagnosed before 20 weeks gestation or hypertension persistent after 12 weeks post partum.

6. Standard dose of magnesium sulphate – The dose of magnesium sulphate used in our setup for treatment for prevention of convulsions in patients with eclampsia and severe preeclampsia. An Intravenous loading dose of 4 grams of magnesium sulphate infusion over 15 to 20 minutes followed by a maintenance dose of 1 gram of magnesium sulphate solution.

7. Therapeutic magnesium levels – Total serum magnesium levels of between 2.0 to 3.5 mmol/L for patients treated with magnesium sulphate as predefined in various studies[10,20]

8. Subtherapeutic serum magnesium levels – Total serum magnesium levels below 2.0 mmol/L for patients treated with magnesium sulphate as predefined in various studies[10,20]

9. Toxic magnesium levels – Total serum magnesium levels of above 3.5 mmol/L for patients treated with magnesium sulphate as predefined in various studies[10,20]

10. Body mass Index (BMI) – the weight of a person in kilograms divided by the square of the height in meters.

11. Occurrence of convulsions - Convulsions in patients despite treatment with the standard dosing regimen of magnesium sulphate used in the two hospitals.

12. Failure of therapy – Occurrence of convulsions in patients despite treatment with standard dosing regimen of magnesium sulphate used in the two hospitals.

**ABBREVIATIONS**

| | |
|---|---|
| ACOG | - American College of Obstetrics and Gynecology |
| BMI | - Body mass Index |
| Et al. | - and others |
| Gms | - Grams |
| Gynaecol | - Gynaecology |
| Hrs | - Hours |
| IM | - Intra Muscular |
| IUGR | -Intra uterine growth retardation |
| IV | - Intra Venous |
| J | - Journal |
| KNH | - Kenyatta National Hospital |
| M MED | - Master of Medicine |
| $Mg2^{+}$ | - Magnesium ions |
| $MgSO_4$ | - Magnesium Sulphate |
| Mmol/L | - Millimoles per Litre |
| Obstet | - Obstetric |
| PMH | - Pumwani Maternity Hospital |
| PPH | - Post Partum Hemorrhage |
| SD | - Standard Deviation |
| SHO | - Senior House Officer |
| UON | - University Of Nairobi |
| WHO | - World Health Organisation |

**ABSTRACT**

Maternal mortality and morbidity in eclampsia is directly related to the number of convulsions thus optimum prevention of convulsions in eclampsia and severe pre-eclampsia is vital. Magnesium sulphate has been shown to be to be supreme in control of these convulsions but despite this, a number of patients continue to convulse during therapy. Studies done show that the levels of serum magnesium achieved during treatment with magnesium sulphate dose regimen vary depending on the body mass index and that patients with higher body mass index do not achieve therapeutic levels. It is thus prudent to determine the serum levels of Magnesium in patients treated with magnesium sulphate to determine the frequency of subtherapeutic levels and whether this contributes to the recorded failure to control convulsions seen in some of these patients.

*OBJECTIVE:*

To determine if sub-therapeutic levels of serum magnesium in patients with severe preeclampsia/eclampsia on treatment with magnesium sulphate are associated with occurrence of convulsions.

*METHODOLOGY:*

This was a prospective cohort study of patients in two serum magnesium categories (therapeutic and subtherapeutic magnesium levels) on treatment with magnesium sulphate for severe preeclampsia and eclampsia. A baseline survey of magnesium levels after administration of the loading dose (4 grams over 5 to 15 minutes as per the protocol) was done at recruitment was done and 101 patients with subtherapeutic levels and 69 with therapeutic levels were followed up to determine the occurrence of convulsions.

*RESULTS*

With the magnesium sulphate regimen of 4 grams loading dose and a maintenance dose of 1 gram hourly that was used in the study 101(59.4%) of the 170 patients with severe preeclampsia/eclampsia had subtherapeutic levels while 69(40.6%) of them had therapeutic levels. Of the patients who convulsed while on these standard dosing regimen, 78.1% had subtherapeutic serum magnesium levels while 21.9% had therapeutic serum magnesium levels. The odds for convulsions for patients with subtherapeutic serum magnesium levels was 2.91 that for those patients with therapeutic serum magnesium levels ( 95% CI 1.10 to 7.98, $p = 0.016$). The body mass index was inversely proportional to the serum magnesium levels and the two were highly correlated ($p<0.05$). The odds of subtherapeutic serum magnesium levels with a high BMI (Overweight or more) was 86.5 times that for those patients with a normal BMI ( 95% CI 13.6-355.5 , $p = 0.001$).

*CONCLUSIONS*

The standard dose regimen of magnesium sulphate used of 4 grams loading dose and 1 gram hourly for maintenance failed to give therapeutic levels of serum magnesium in a majority of patients. Many of the patients who convulsed while on treatment with magnesium levels had subtherapeutic serum magnesium levels. A high body mass index in the patients was associated with subtherapeutic levels.

*RECOMMENDATIONS*

Studies testing drug regimens based on body mass index or higher doses should be formulated with a goal to improve the control of convulsions in patients with eclampsia/severe eclampsia.

# INTRODUCTION AND LITERATURE REVIEW

Eclampsia is a significant cause of maternal and perinatal morbidity and mortality [1,2,3,4] and is more prevalent in developing countries. The incidence of eclampsia has been relatively stable at 4 to 5 cases per 10,000 live births in developed countries [5]. In developing countries, however, the incidence varies widely from 6 to 100 per 10,000 live births [1] and accounts for about 50,000 maternal deaths annually. The prevalence of preeclampsia in Kenyatta National Hospital was found to be 5.6% in a study by Kamau[3]. Chege in a study on patients with eclampsia in KNH found a high maternal morbidity with 4.5% of the study patients requiring admission to the intensive care unit. Perinatal mortality and morbidity was also high for babies born to these mothers with 64% requiring Neonatal Unit admission and 23% deaths[4]

The pathogenesis of eclamptic seizures is poorly understood. Proposed etiologies include cerebral vasospasm with local ischemia/infarction and cytotoxic (intracellular) edema and hypertensive encephalopathy with hyperperfusion, vasogenic (extracellular) edema, and endothelial damage [6,7]. In the vasospasm theory there is cerebral overregulation in response to high systemic pressure resulting in cerebral underperfusion and in the hyperperfusion theory mentioned above, there is loss of autoregulation of cerebral blood flow in response to high systemic pressure resulting in hyperfusion. There is poor correlation between occurrence of seizures and severity of hypertension. Seizures may occur with insignificant blood pressure elevations that are only slightly higher than readings recorded 24 hrs previously. The hallmarks of hypertensive encephalopathy are very infrequent in eclampsia, where fundoscopic changes are minimal [8].

**Magnesium sulphate**

$MgSO_4$, was first used to prevent eclamptic seizures in 1906 by Horn in Germany, who injected it intrathecally. An intramuscular regimen was used in 1926 to prevent recurrent seizures in women with eclampsia and the drug was given intravenously in 1933 to women with pre-eclampsia and eclampsia [9]. Despite its early use, the use of

$MgSO_4$ continued to be controversial. The Collaborative Eclampsia Trial [10] provided irrefutable evidence of the superiority of $MgSO_4$, when compared to diazepam and phenytoin in the prevention of recurrent seizures in women with eclampsia. A Cochrane review [11] found that magnesium sulphate was safer and more effective than lytic cocktail (a mixture of chlorpromazine, promethazine and pethidine) for the prevention of repeat seizures in eclamptic women. Chege[4] in his study also confirmed the effectiveness of magnesium sulphate over diazepam in preventing recurrent convulsions in eclamptic women.

In the multinational Eclampsia collaborative trial [10] eclamptic women were randomly allocated to magnesium sulphate, diazepam and phenytoin. In the $MgSO_4$ versus phenytoin group, 22 out of 388(5.7%) had recurrent convulsions on magnesium compared to 66 out of 387(17.1%) in the phenytoin group. In the $MgSO_4$ versus diazepam arm 60 out of 453(13.2%) convulsed while on $MgSO_4$ while 126 out of 452(27.9%) convulsed while on diazepam. The collaborative group concluded that there was compelling evidence in favor of magnesium sulphate rather than diazepam or phenytoin for treatment of eclampsia. Both Intravenous and intramuscular regiments of $MgSO_4$ were used in the trial with no difference in outcomes for either regimes. In a study done by Chege[4] in KNH comparing outcomes of eclamptic patients treated with $MgSO_4$ versus diazepam, more patients had seizures while on diazepam 16 out of 134(16%) compared to 13 out of 134(9.7%) on $MgSO_4$.

Several randomized clinical trials have shown a significant reduction of eclampsia in severe pre eclampsia given magnesium sulphate. In a study by Lucas et al [12] in which women with preeclampsia were allocated to receive magnesium sulphate (a regimen which consisted of a 10-g intramuscular loading dose followed by a maintenance dose of 5 g given intramuscularly every four hours) vs. phenytoin. No women of the 1089 in the magnesium sulphate arm developed convulsions while 10 of the 1049 in the phenytoin arm developed convulsions. In the larger Magpie trial[5] more than 10,000 women with pre eclampsia were randomly allocated to magnesium sulphate or placebo. Women allocated to the magnesium sulphate arm had a 58 percent lower risk of eclampsia than

placebo. The use of $MgSO_4$ for prophylaxis of convulsions in severe pre-eclampsia has been rising steadily in KNH. Currently $MgSO_4$ is used locally for prophylaxis in most patients with severe pre-eclampsia. According a study by Kamau [3] $MgSO_4$ as prophylaxis in severe pre-eclampsia was only used in 1.3% for the period of 2000 to 2005 in KNH

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**Mechanism of action of Magnesium sulphate**

The mechanism of action of magnesium sulphate as an anticonvulsant in pre-eclampsia/eclampsia is not clearly understood. Magnesium sulphate decreases the amount of acetylcholine released at neuromuscular junction, resulting in peripheral neuromuscular blockade at high magnesium concentration, though this does not account for its anticonvulsant effect[9]. Researchers have speculated that magnesium ion also acts by blocking calcium entry into neurons through the N-methyl-D-aspartame (NMDA) receptor-operated calcium channel which is epileptogenic [9]. Doppler studies of brain flow in preeclamptic women suggest that magnesium sulphate vasodilates the smaller diameter intracranial vessels distal to the middle cerebral artery and may exert its main effect in the prophylaxis and treatment of eclampsia by reversing vasospastic cerebral ischemia[9]. Other possibilities include inhibition of platelet aggregation and protection of endothelial cells from damage by free radicals.

Magnesium sulphate may be given intravenously by continuous infusion or intramuscularly by intermittent injections[12]. Pritchard popularized the intramuscular regimen while Zuspan formulated the continuous intravenous regimen[13]. In the intramuscular regimen, a continuous intravenous loading dose of 4 g (usually in 20% solution) is given over five minutes (preferably 10-15 min) followed immediately by 5 g (usually in 50% solution) as a deep intramuscular injection into the upper outer quadrant of each buttock. Maintenance therapy is in the form of a further 5 g intramuscularly every four hours, to be continued for 24 hours after the last seizure. Alternatively the intravenous regimen involves a loading dose of 4 g intravenously (5 g is used in some centres) which is followed by an intravenous infusion of 1- 2 g/h continued for 24 hours after the last fit. If convulsions recur, both regimens advocate a further 2-4 g (depending

on the woman's weight, 2 g if < 70 kg) to be given intravenously over five minutes. In the WHO schedule which is also used in Kenyatta and also Pumwani Maternity Hospital, the above regimens are used with 1g/hr being used for maintenance in the intravenous regimen. Studies by Sibai et al [14] comparing intravenous versus intramuscular magnesium sulphate found no significant difference in mean magnesium levels.

Controversy exists regarding the optimum maintenance dose. An infusion of 1 g/h was used in the collaborative trial, but some authors have advocated 2 g/h and 3g/hr in some patients. Sibai et al [15] evaluated several modifications of the continuous intravenous regimen in order to achieve acceptable serum magnesium levels throughout the infusion. During a 21-month period, the authors encountered 13 patients who developed seizure activity while receiving intravenous $MgSO_4$. Serum magnesium levels at the time of seizure were below the therapeutic range in 11 of the 13 patients. Random serum $Mg^{2+}$ samples were obtained from 120 patients treated with intravenous $MgSO_4$ for pre eclampsia and eclampsia. The samples were collected 2 to 48 hours after the loading dose and while the patients were on a maintenance dose of 1, 2, or 3 g/hr. When a maintenance dose of 1 or 2 g/hr was used, 98 and 50% of the respective serum magnesium values were below levels considered therapeutic by several authors. Therapeutic levels were achieved in all patients receiving a maintenance dose of 3 g/hr. In conclusion it was felt that the best regimen was a 6 g loading dose followed by a maintenance dose of 2 g/h.

**$MgSO_4$ pharmacokinetics**

Magnesium sulphate USP is $MgSO_4 . 7H_2O$. After its administration, about 40% of plasma magnesium is protein bound. The unbound magnesium ion diffuses into the extra vascular-extracellular space, into bone, and across the placenta and fetal membranes and into the fetus and amniotic fluid. In pregnant women, apparent volumes of distribution usually reach constant values between the third and fourth hours after administration, and range from 0.250 to 0.442 dl/kg. An intravenous loading dose of 4 g to 6 g results in an immediate but transient increase with an average peak level at 60 minutes. At a constant rate of infusion serum levels plateau when the rate of urinary excretion of magnesium

equals the rate of infusion. With an infusion of 1 gram/hr, $MgSO_4$, levels plateau after 24 hours [9]. Various authors [9,16,17] observed that the concentration of magnesium in plasma rises gradually after intra muscular injections, with 90-120 minutes being the usual time required to reach maximal levels in plasma, and indeed, that was the basis for initiating therapy with the intravenous dose. Magnesium is excreted almost solely by the kidney and after four hours about 50% of the infused dose is excreted in the urine with a mean half life of 4.66 hrs [9]. Seventy five percent of the infused dose is excreted during the infusion and by 24 hours after the infusion 90% of the magnesium has been eliminated.

Data from Sibai et al [15] suggests that levels are consistently < 1.7 mmol/L using a regimen of 1 g/h for maintenance (used in the collaborative trial). In contrast, mean serum levels range is from 1.7 to 3.3 mmol/L when a maintenance infusion of 2 g/h is used. Although there is no single accepted therapeutic level of magnesium, the therapeutic range is considered to be between 2 and 3.5 mmol/L [9]. The first warning of impending toxicity in the mother is loss of the patellar reflex at plasma concentrations between 3.5 and 5 mmol/L. Respiratory paralysis occurs at 5 to 6.5 mmol/L. Cardiac conduction is altered at greater than 7.5 mmol/L, and cardiac arrest can be expected when concentrations of magnesium exceed 12.5 mmol/L. Careful attention to the monitoring guidelines can prevent toxicity. Deep tendon reflexes, respiratory rate, urine output and serum concentrations are the most commonly followed variables [13]. Treatment with calcium gluconate, 1 g intravenously along with withholding further magnesium sulphate usually reverses mild to moderate respiratory depression. Unfortunately the effects of this intravenous calcium gluconate are short lived and prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium are uncommon[13].

Studies by Dayicioglu et al [18] in which magnesium levels were measured after infusion of a standard magnesium sulphate infusion protocol, found that magnesium levels in the majority of patients inversely correlated with the body mass index. They also found out that sub therapeutic levels were found particularly in women whose body mass index

exceeded 30 and in these patients a higher maintenance dose of 2 – 2.5g/hr would be more appropriate in maintaining the doses. Another study by Ekele et al in Nigeria [19] in which magnesium sulphate levels after administration of Magnesium sulphate using the modified Pritchard regimen were measured found that the magnesium level 4 hours after the loading dose was 1.95 mmol/L which was the lower limit of normal though it was speculated that the relatively low BMI (21.9) contributed to the control of seizures despite the relatively low serum levels found. In another study done by Aali et al [20] in which fifty singleton patients with severe pre eclampsia/eclampsia received a loading dose of 4 g of magnesium sulfate, followed by 2 g per hour as maintenance dose until 24 hours after delivery or after the last seizure, a level of 4 mEq/L of total magnesium was not obtained (below therapeutic range) in up to 42% of patients during the treatment.

Studies have also been done testing lower than recommended doses for patient populations with average lower weights. In a study done by Sardesai et al [21] using a low dose protocol intra muscular regimen in which the maintenance dose was reduced to 2g every four hourly instead of the 5g used in the Prichard regime, the average serum magnesium levels were found to be 4.89 mg/dl which is within therapeutic range. It was postulated that the therapeutic levels were maintained despite this low dosing because on average the Indian women were smaller – the average weight being 48.4 kg. A similar study was done using a low dose $MgSO_4$ regimen "Dhaka" for the smaller Bangladeshi patients [22] where the intramuscular maintenance dose of 5g(used in the Prichard regime) was halved to 2.5g every four hours. With this dose the mean serum magnesium level was 3.87 mg/dl with only one patient out of 65 developing convulsions, which was just slightly below the therapeutic range for some patients.

Because magnesium is cleared almost exclusively by renal excretion, plasma magnesium concentration using the doses described previously is excessive if glomerular filtration is decreased substantively. The initial standard dose of magnesium sulphate can be administered without the knowledge of renal function. Renal function is thereafter estimated by measuring plasma creatinine and whenever it is 1.3 mg/dl or higher, only half of the maintenance intramuscular magnesium sulphate dose discussed earlier is

given. With this dosage the serum magnesium levels remain 4 – 7 mEq/L[20]. When magnesium sulphate is being given by continuous infusion serum magnesium sulphate must be used to adjust the dosage and in both regimens periodical magnesium sulphate should be done [9].

## RATIONALE/JUSTIFICATION OF THE STUDY

Prevention of convulsions in severe pre eclampsia and eclampsia is important in reducing maternal mortality and morbidity associated with the condition. Magnesium sulphate is the drug of choice for control of convulsions in eclampsia/ severe preeclampsia with proven efficacy over previously used treatments as proven by the eclampsia collaborative trial. Occurrence of seizures in eclamptic patients while on $MgSO_4$ therapy has been reported to be 10 – 15%. In a retrospective study comparing the efficacy of magnesium sulphate to that of diazepam in Kenyatta National Hospital in 2004 it was reported that 9.7% of patients convulsed while on magnesium sulphate therapy. Therapeutic levels of magnesium are considered to be between 2.0 to 3.5 mmol/L by for control and prevention of convulsions in eclampsia and severe preeclampsia. Various studies done found that a significant proportion of patients treated with various dosing regimens of magnesium sulphate had subtherapeutic levels of serum magnesium. Another study found that serum magnesium levels were inversely related to the body mass index in patients on treatment with magnesium sulphate. It was thus important to determine whether occurrence of convulsions in patients on treatment with magnesium sulphate was due to subtherapeutic levels and to determine what other patient characteristics influenced these levels.

## RESEARCH QUESTION

Is there a causal relationship between the serum magnesium levels in patients with severe preeclampsia/eclampsia on treatment with magnesium sulphate and the occurrence of convulsions.

## NULL HYPOTHESIS

There is no association between subtherapeutic serum magnesium levels in patients with severe preeclampsia/eclampsia on treatment with magnesium sulphate and occurrence of convulsions.

## OBJECTIVES

### *Main Objective*

To determine if sub-therapeutic levels of serum magnesium in patients with severe preeclampsia/eclampsia on treatment with magnesium sulphate are associated with occurrence of convulsions.

### *Specific Objectives*

1. To determine the mean levels of serum magnesium in patients treated with $MgSO_4$ for eclampsia and severe pre-eclampsia.
2. To determine and compare the frequency of occurrence of convulsions in those with sub-therapeutic and therapeutic levels of serum magnesium.
3. To determine patient characteristics that are associated with abnormal serum magnesium levels.

## MATERIALS AND METHODS

### *Study design*

This was a prospective cohort study of patients in two serum magnesium categories (therapeutic and subtherapeutic magnesium levels) on treatment with magnesium sulphate for severe preeclampsia and eclampsia. A baseline survey of magnesium levels

after administration of the loading dose(4 grams over 5 to 15 minutes as per the protocol) was done at recruitment was done and 101 patients with subtherapeutic levels and 69 with therapeutic levels were followed up to determine the occurrence of convulsions.

***Study period***

The study period was from May 2008 to September 2008 when the sample size was attained.

***Study area***

The study was conducted in the maternity wards of Kenyatta National and Pumwani Maternity Hospitals. Kenyatta National Hospital is the main referral hospital in Kenya and teaching facility for University of Nairobi Medical School. It offers both specialized and non specialized services. The maternity unit comprises of a busy labour ward, labour ward theatre, 3 lying – in wards, gynecological ward and an acute gynecology ward. It is run by senior house officers from the University of Nairobi under supervision from a team of consultants from the University of Nairobi and Kenyatta National Hospital. The labour ward has an admission unit, 10 first stage rooms, a 3 bed acute room, 2 second stage rooms and a $4^{th}$ stage room. Patients are registered at the admission desks and are all assessed by a senior house officer (SHO). Those in labour are admitted into first stage of labour or into second stage of labour while those not in labour requiring monitoring or awaiting procedures are admitted into the lying – in wards. Those requiring acute management are admitted to the acute room for more intensive monitoring and care.

Pumwani Maternity Hospital is located 2 kilometers East of Nairobi Central Business District. It is the largest maternity hospital in East and Central Africa with daily average deliveries of 70 and an average annual delivery rate of 30,000. It has five post natal wards, one antenatal ward and a labour ward. It serves as mainly the low and medium income population and serves a referral centre for various city council health centers.

*Study population*

The study population comprised of 170 patients – 74 with severe pre-eclampsia and 96 with eclampsia on treatment with a standard dose of magnesium sulphate in the maternity wards of KNH and Pumwani maternity hospital. Those patients fulfilling the inclusion criteria who consented or for whom consent was given were consecutively recruited into the study till the sample size was obtained.

**Inclusion criteria:**

- Patients with eclampsia or severe preeclampsia on $MgSO_4$ therapy . The criteria for severe preeclampsia was those with fitting the definition with :
  - visual disturbances
  - persistent severe epigastric pains
  - Severe persistent headaches
- Patients on the intravenous $MgSO_4$ regimen (WHO Protocol).
- Patients able to consent or those for who consent has been given.

**Exclusion criteria**

- Patients with convulsions due any other causes.
- Patients on intramuscular $MgSO_4$ regime(WHO regime).
- Patients who have been given any other medication for control of convulsions prior to admission or where it is not possible to clearly establish that no other medication had been given

*Sample size*

The sample size was calculated with the following formula to determine the sample size

$$N = \frac{\{Z\alpha 1_2 \sqrt{2P(1-P)} + Z\ 1-\beta \sqrt{P_1(1-P_1)+P2(1-P_2)}\}^2}{(P_1-P_2)^2} \qquad [27]$$

$Z\alpha 12$ =(95% confidence interval)= 1.96

$Z\ 1-\beta$= (80% power)=0.842

The rate of convulsions while on MgSO4 has been documented to be 10 – 15% [2](without determination on whether the levels were therapeutic or not)

P1= proportion of event in the exposed group(with subtherapeutic magnesium levels) 15% convulsion rate was assumed in the exposed group.

P2= Proportion of event in the un – exposed group (with therapeutic magnesium levels). A 5% convulsion rate was assumed in the un-exposed group

P= (P1+P2)/2

A ratio of 1:1 for both groups of the study : those with therapeutic levels of serum magnesium and that with sub- therapeutic levels of serum magnesium

N= 57 (each arm)

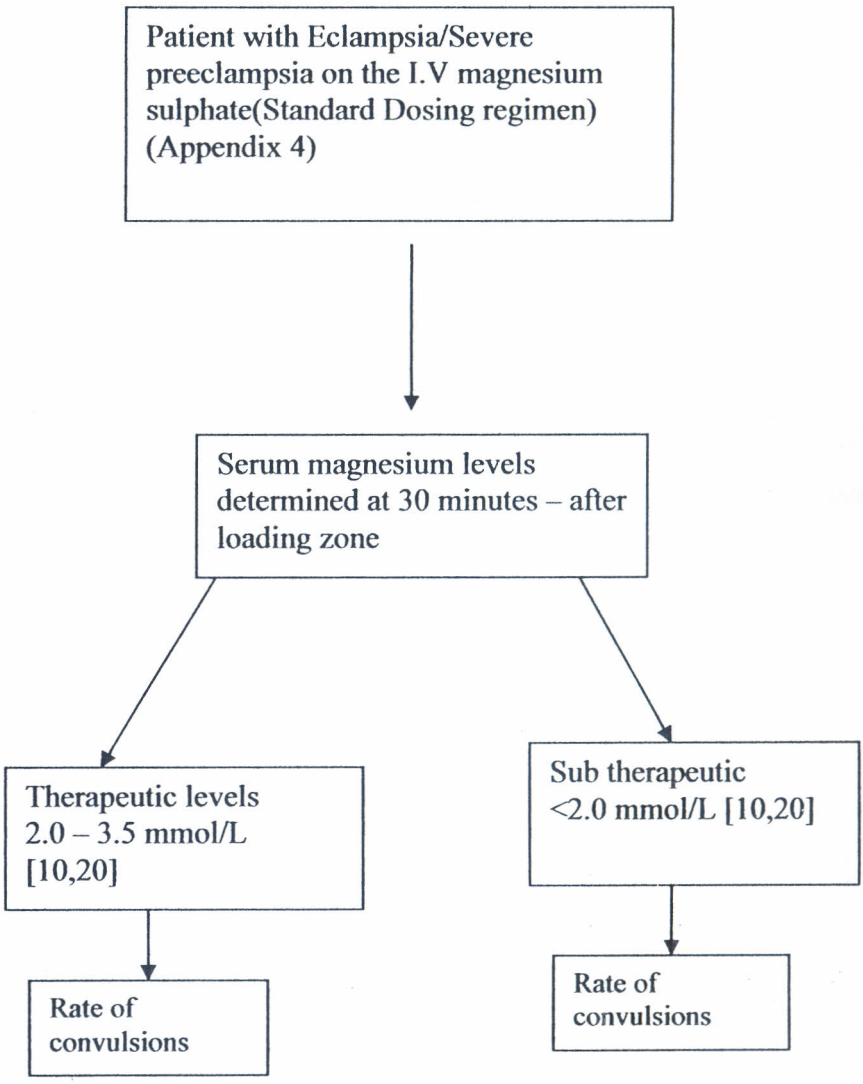
Sample size of **64** per group allowing a 10% fall out rate was adequate to detect significant difference in the two arms of serum magnesium levels.

**Recruitment, Data Collection**

The patient's particulars were filled in a **data collection form** ***(appendix 2)*** by the investigator or study assistants after a detailed consent ***(appendix 1)*** form was read to or by the patient or relatives. After the patient or relative gave a signed consent, the following particulars were be recorded; Patients name socio-demographic details were filled out - IP No, Age, Marital status, Education level, occupation weight and height. The reproductive health characteristics were also filled out – the gestation in weeks, Parity and the labour status. The disease characteristics were also filled such as the blood pressure at admission, the temperature, number of convulsions, the presence of severe headaches, blurring of vision(visual scotomas), epigastric pain, deranged liver and kidney function. The drug administration details were also filled out including the time of administration of the loading dose and the dose given, time and amount of maintenance doses of magnesium sulphate. Laboratory values were filled out including the serum magnesium level at 30 minutes, the serum magnesium level at 4 hours and the serum magnesium level at 24 hours. The clinical findings were also recorded such as the presence and number of convulsions during administration, the hourly respiratory rate, the presence or absence of deep tendon reflexes and the urine output.

The height and weight were taken at the time of admission if the patient was in a stable clinical condition. For those who were comatose, this was taken at the earliest opportunity after recovery of conscience. Blood pressure and temperature were also taken at the time of admission. An initial blood samples was drawn from the patient 30 minutes the magnesium sulphate loading dose infusion had been started and sample taken to the laboratory for determination of the serum magnesium level. This level was used to classify the patient as either having therapeutic levels or subtherapeutic levels. In case of any continued convulsions despite this standard dosing regimen at any time during therapy the patient was treated with an additional loading dose of 2 to 4 grams of magnesium sulphate intravenous bolus over 15 to 20 minutes as is stated in the regimen. Later on a second sample of blood was drawn after 4 hours and again a third after 24 hours for determination of serum magnesium during those times. The drawing of samples has been explained in the section below on *sampling procedure*. Clinical parameters such as blood pressure, temperature, respiratory rate, patellar reflexes and urine output were monitored hourly as is usual for patients on magnesium sulphate therapy and recorded. In addition a blood slide for malaria and random blood sugar were taken to rule out continued convulsions due to other causes. Observations were made on occurrence of convulsions during the next 48 hours and treated as above.

*A Schematic Diagram Of The Study Flow*



**Blood sampling procudure**

Venous blood were drawn from each patient from the contra lateral arm away from that in which the magnesium sulphate infusion is being given at the following times:

1. The loading dose is given as a slow intravenous push over 10 to 15 minutes. The first sample was taken after 30 minutes have elapsed since the beginning of the intravenous administration of the loading dose. This gave time for equilibration of the drug and this method had also been used in other similar studies studying the peak levels achieved after the loading dose of $MgSO_4$ [18,19].
2. The maintenance doses of magnesium were given in a continuous infusion of 1g per hour. 4g of magnesium sulphate (100 mls of solution) is added to 400 mls of n/saline. The infusion was then given at 125 mls per hour to give an infusion of 1 gm per hour. This had been calculated to be 30 drops per minute infusion.

a) Blood was drawn immediately at the end of 4 hours after the infusion of the second preparation was finished before connection of the next preparation.
b) The last sample at 24 hours was drawn immediately after the last preparation of $MgSO_4$ has been given.

Venous blood samples were drawn at the times described above, with the sample being appropriately marked with the patient number and the time of collection (which were all coded). Two millimeters of blood was drawn using a needle and syringe then transferred to a plain bottle. The sample was then allowed to clot and then centrifuged at 3000 rpm for 10 minutes. 1.0 ml of serum was transferred into a serum vial for chemical analysis. In case of the need for storage the separated serum was be refrigerated at -20° centigrade and below.

***Analysis of samples***

Total magnesium was determined using an automated colorimeter in the Renal Department laboratory using a chemistry analyzer (Technicon RA-1000) using assay kits manufactured by Randox Laboratories. Analysis is done through a colorimetric method in which Magnesium ions react in alkaline media with a metallochrome dye Calmagite to

form a chromophore which absorbs light at 500 nm. Calcium is excluded by complexing with EGTA.

***Data analysis and presentation***

A standard data collection form was used to collect all the data generated in the study. See appendix 2. Data was entered, cleaned and verified. Analysis was done using the SPSS software version 12. 0.1 for windows. A comparison between the two groups was performed with chi-square tests (or fisher's exact test where appropriate). A probability value of $P < 0.05$ was considered statistically significant. Odds ratios and their confidence intervals were also calculated. The analyzed data will be summarized into histograms, pie charts, tables and graphs.

***Study limitations***

1. The study combined patients with severe preeclampsia and those with eclampsia and the risks of convulsing for the two patient populations is different. This weakness is circumvented by a sub analysis of occurrence of convulsions in the two different groups as well as in the whole group.
2. Problems in data collection could have affected the quality of data such as inaccurate recording, delays in drug administration and in analysis of samples that would cause higher serum values after hemolysis. This problem was circumvented and in rejection of data where there were obvious errors in data collection.
3. Pretreatment number of convulsions could have been a confounder and affected the risk of recurrence of convulsions in patients with convulsions. However the association between the occurrence of convulsions no of pretreatment convulsions was not significant.
4. For referred patients any treatment that might have been given and not indicated in the referral notes may have affected the outcomes though every effort was made to determine this.
5. The various criteria for severe preeclampsia could affect the relative risk of progression to convulsive disoders with some factors being more likely to

increase the risk of convulsions. For example patients with visual scotomata might be at a higher risk of convulsing that those with other criteria such as those with thrombocytopenia. To cater for this problem, only those patients with severe preeclampsia at a high risk of convulsing were enrolled(with signs of impending eclampsia – visual disturbances, severe headache and epigastric pains).

6. The levels of proteinuria here mentioned are random samples and not quantitative measurements which would be more accurate due to the difficulty and expense of a 24 hour urine specimen collections.

***Ethical considerations***

The following were addressed to before conducting the study and during the data collection:

1. Approval was sought and received from the ethics and research committees of Kenyatta National/Nairobi University and Pumwani Maternity Hospitals. There was no added risk or cost to the patient.
2. Approval was sought from the Kenyatta National Hospital / University of Nairobi Ethics and Research committee and the Hospital board of Pumwani Maternity Hospital.
3. The purpose of the study was explained verbally and an informed written and verbal consent was obtained from the study participants.
4. Enrollment to the study was voluntary and any decision that the patient took in this respect had no bearing on the medical care that they received. No treatment was withheld from the patient because of declining to participate in the study.
5. Records were safely kept and study numbers rather than names were used to ensure confidentiality of information.

During the study the infusion rate of the drug was not increased if the levels were found to be suboptimal. This would have been an ethical concern but to circumvent it this, a supplemental dose was given incase of any further convulsions as the protocol states.

## RESULTS

The study group consisted of 170 patients with Eclampsia (96) and severe preeclampsia(74) treated with Magnesium Sulphate at a loading dose of 4 grams and a maintenance dosing of 1 gram at Kenyatta National and Pumwani Maternity hospitals. Of these 101 patients had subtherapeutic serum magnesium levels and 69 had therapeutic serum magnesium levels.

**Table 1 Socio-demographic and obstetric characteristics of the study population.**

| Characteristic | Subtherapeutic level (< 2.0 mmol/l) (N=101) | Therapeutic level (2.0 – 3.5 mmol/l) (N=69) | P value |
|---|---|---|---|
| **Age in years** | | | |
| < 19 years | 20 (19.8%) | 14 (20.3%) | P=0.119 |
| 20 – 24 yrs | 25 (24.8%) | 27 (39.1%) | |
| 25 – 29 yrs | 29 (28.7%) | 15 (21.7%) | |
| 30 – 34 yrs | 13 (12.9%) | 10 (14.5%) | |
| >= 35 yrs | 14 (13.9%) | 3 (4.3%) | |
| **Education level** | | | |
| No formal education | 7(6.9%) | 3(4.3%) | P=0.858 |
| Primary level | 56(55.4%) | 38(55.1%) | |
| Secondary level | 29(28.7%) | 20(29.0%) | |
| College/university | 9(8.9%) | 8(11.6%) | |
| **Marital status** | | | |
| Single | 20 (19.8%) | 10 (14.5%) | P=0.418 |
| Married | 81 (80.2%) | 59 (85.5%) | |
| **Occupation** | | | |
| House wife | 62 (61.4%) | 43 (62.3%) | P=0.516 |
| Employed | 39 (38.6%) | 26 (37.7%) | |
| **Parity** | | | |
| 1 | 38(37.6%) | 32(46.4%) | P=0.468 |
| 2 – 4 | 58(57.4%) | 35(50.7%) | |
| >= 5 | 5(5.0%) | 2(2.9%) | |
| **Gestation by dates** | | | |
| 20 - 27 wks | 6(5.9%) | 5(7.2%) | P=0.400 |
| 28 - 36 wks | 54(53.5%) | 43(62.3%) | |
| >= 37 wks | 41(40.6%) | 21(30.4%) | |
| **Pregnancy status** | | | |
| Ante partum | 44(43.6%) | 24(34.8%) | P=0.356 |
| Intrapartum | 47(46.5%) | 34(49.3%) | |
| Post partum | 10(9.9%) | 11(15.9%) | |

Table 1 shows the socio-demographic and reproductive health characteristics of the study population. There was no significant difference in the two serum magnesium groups in terms of age, educational level, marital status, occupation, parity and pregnancy gestation by dates. There was also no significant association between the above socio-demographic and reproductive health characteristics with the serum magnesium levels.

**Table 2 Disease characteristics of the study population**

| Characteristic | Subtherapeutic level (< 2.0 mmol/l) (N= 101) | Therapeutic level (2–3.5 mmol/l)(N=69) | P value(0.05) |
|---|---|---|---|
| **Diastolic Blood Pressure(mm Hg)** | | | |
| 90-109(Mild Hypertension) | 33(32.7%) | 23(33.3%) | P=0.928 |
| >=110(Severe hypertension) | 68(67.3%) | 46(66.7%) | |
| **Systolic Blood Pressure(mm Hg)** | | | |
| 140-159(Mild hypertension) | 16(15.8%) | 15(21.7%) | P=0.328 |
| >=160(Severe Hypertension) | 85(84.2%) | 54(78.3%) | |
| **Proteinuria Level** | | | |
| 1+ | 4(4.0%) | 0 | P=0.261 |
| 2+ | 45(44.6%) | 27(39.1%) | |
| 3+ | 33(32.7%) | 29(42.0%) | |
| 4+ | 19(18.8%) | 13(18.8%) | |
| **Eclampsia/Severe preeclampsia** | | | |
| Eclampsia | 55(54.5%) | 41(59.4%) | P=1.217 |
| Severe Preeclampsia | 46(45.6%) | 28(40.6%) | |

Table 2 shows the various disease characteristics in the two groups of serum magnesium. The two groups were not significantly different in terms of disease characteristics namely severity of hypertension or proteinuria. The severity of hypertension and proteinuria level was also not significantly associated with the serum magnesium level categories.. The number of patients who had eclampsia or severe eclampsia was also not significantly different in the two serum magnesium groups.

**Table 3 Serum Magnesium Levels on follow – up at 4 hours and at 24 hours**

| Serum magnesium levels | Time of follow - up | |
|---|---|---|
| | 4 hours | 24 hours |
| Subtherapeutic levels (<2.0 mmol/L) | 94(55.3%) | 82(48.2%) |
| Therapeutic Levels (2.0 – 3.5 mmol/L) | 76(44.7%) | 88(51.8%) |
| **Total** | 170(100%) | 170(100%) |

Table 4 shows the serum magnesium levels during follow-up of the two study populations classified as either subtherapeutic or therapeutic at onset (after the loading dose of magnesium sulphate). There is a progressive decrease in the proportion of patients having subtherapeutic levels with time. After 4 hours of follow-up the proportion having subtherapeutic levels had decreased to 55.3% After 24 hours of follow-up the proportion with subtherapeutic levels had fallen to 48.2%

**Table 4 Mean serum magnesium levels during follow - up**

| Time | Mean serum magnesium levels(SD) |
|---|---|
| After loading dose | 1.85 mmol/L (0.32) |
| 4 hours follow - up | 1.93 mmol/L(0.28) |
| 24 hour follow – up | 1.98 mmol/L(0.21) |

Table 4 shows the mean serum magnesium levels during follow-up. There is a progressive rise in the mean levels over the follow – up period. The mean serum magnesium level after loading dose was 1.85 mmol/L and rose during the 4 hour and 24 hour follow up periods to 1.93 mmol/L and 1.98 mmol/L respectively.

**Table 5 Serum magnesium levels by occurrence of convulsions**

| Serum Magnesium Levels | Occurrence of convulsions | | |
|---|---|---|---|
| | Yes | No | |
| Subtherapeutic levels(<2.0 mmol/Lt) | 25(78.1%) | 76(55.1%) | OR(95% CI) |
| Therapeutic Levels (2.0 – 3.5 mmol/Lt) | 7(21.9%) | 62(44.9%) | 2.91(1.10-7.98) |
| Total | 32(100%) | 138(100%) | P=0.016 |

There was a significant association between the levels of serum magnesium and occurrence of convulsions, $p< 0.05$ ($X^2 = 5.72$, df = 1). Of all the patients who convulsed 78.1% were in the subtherapeutic category against only 21.9% who were in the therapeutic group. The odds of convulsions with subtherapeutic levels was 2.91 with a Confidence interval of 1.10 to 7.98.

**Table 7 Association between BMI categories and Serum magnesium levels**

| BMI categories | Serum level groups | | Totals |
|---|---|---|---|
| | Subtherapeutic (<2.0 mmol/l) | Therapeutic (2 - 3.5 mmol/l) | |
| Overweight – Obesity(>25) | 100 | 37 | 137 |
| Normal BMI(18.6 – 25) | 1 | 32 | 33 |

The association between the BMI categories and the serum magnesium was investigated and is illustrated in the above 2 by 2 table. There was a highly significant association between the serum magnesium level and the BMI category, $p<0.001$ ($X^2 = 72.973$, df = 3). The odds of having subtherapeutic levels of serum magnesium when the BMI is more than 25 is 86.5 times that for whom the BMI is normal..

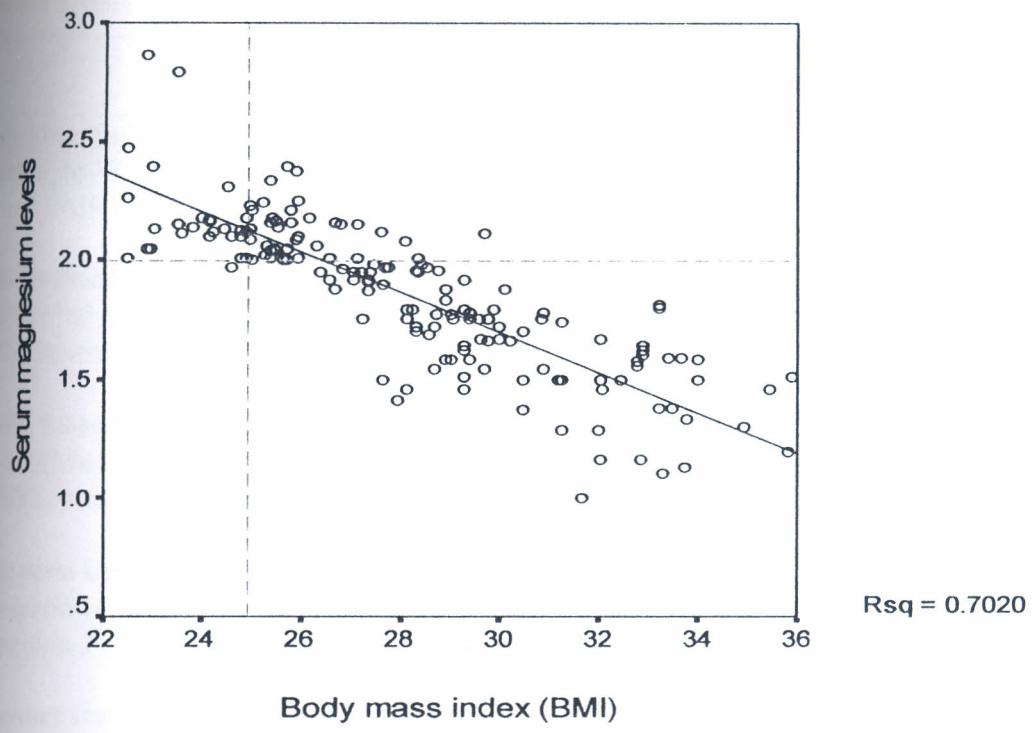



**Fig 1 Correlation between the body mass index and the serum magnesium levels after loading dose**

Figure 1 shows that the serum magnesium levels were inversely correlated with the body mass index. Patients with higher BMI values had lower serum magnesium levels and those with lower BMIs had higher serum magnesium levels. The dashed line on the x-axis delineates the therapeutic margins. Those serum magnesium levels below are subtherapeutic and are the majority while those above are therapeutic. The dashed line of the y –axis delineates the normal BMI level . Those to the left have a normal BMI and those to the right who are majority are overweight and above.

**Table 8 Occurrence of convulsions by various parameters**

| | CONVULSIONS | | | P value |
|---|---|---|---|---|
| | YES | NO | OR(95% CI) | (0.05) |
| **Body Mass Index** | | | | |
| Overweight – Obesity(>25) | 30((93.8%) | 107(77.5%) | 4.35(1.00 – 39.34) | P=0.037 |
| Normal BMI(18.5 – 25) | 2(6.3%) | 31(22.5%) | | |
| **Diastolic Blood Pressure(mm Hg)** | | | | |
| 90-109(Mild Hypertension) | 8(25.8%) | 48(34.8%) | 1.06(0.43-2.65) | P=0.289 |
| >=110(Severe hypertension) | 24(75.0%) | 90(65.2%) | | |
| **Systolic Blood Pressure(mm Hg)** | | | | |
| 140-159(Mild hypertension) | 6(18.8%) | 25(18.1%) | 0.73(0.25-2.28) | P=0.933 |
| >=160(Severe Hypertension) | 26(81.3%) | 113(81.9%) | | |
| **Proteinuria Level Categories** | | | | |
| Proteinuria 1+ and 2+ | 8(25.0%) | 68(49.3%) | 2.41(0.97-6.10) | P= 0.013 |
| Proteinuria 3+ and 4+ | 24(75.0%) | 70(50.7%) | | |
| **Pregnancy status** | | | | |
| Antepartum + Intrapartum | 26(81.3%) | 123(89.1%) | 0.76(0.23-2.59) | P=0.222 |
| Postpartum | 6(18.8%) | 15(10.9%) | | |

Table 8 shows the relationship between occurrence of convulsions against various parameters – body mass index, blood pressure, proteinuria and pregnancy status. There is a significant association between the BMI (Normal BMI/ Over weight and Obesity) and the occurrence of convulsions, $p < 0.05(X^2 = 4.37, df = 1)$. The odds for convulsions for patients with high BMI (Overweight or more) was 4.35 that for those patients with a normal BMI ( 95% CI 1.00 to 39.34 , $p = 0.01$).

In the table there is also a significant association shown between the proteinuria categories and the rate of convulsions $p< 0.05$ ($X^2 = 4.38$, df =1). The odds of failure to control convulsions in patients with elevated proteinuria (3+ and 4+) is 2.41 that for those with lower proteinuria levels of 2+ and less ( 95% CI 0.97 to 6.10, $p = 0.013$).

There was however no significant association found between the severity of hypertension (systolic and diastolic levels) and the occurrence of convulsions during treatment with

agnesium sulphate. The pregnancy status Antepartum, intrapartum versus post partum s also not significantly associated with the risk of failure of control of convulsions with a tandard dose of magnesium sulphate.

## LOGISTICAL REGRESSION MODELS

The association between serum magnesium levels (therapeutic/subtherapeutic) and the main variables BMI and proteinuria levels were investigated in a model by logistical regression.

BMI turned out to have the highest predictive association with the serum magnesium levels having a B value of -1.78 being highly significant in the model.

The association between the occurrence of convulsions and the main variables :- BMI, serum magnesium levels and proteinuria were also investigated in a logistical regression model. In the model serum magnesium levels had the highest predictive score of 18.470 which was highly significant $p<0.001$ followed by proteinuria with a score of 4.921 which was also highly significant $p<0.05$.

## DISCUSSION

In this study, the Zuspan magnesium sulphate regimen of 4 grams intravenous loading dose followed by a maintenance of 1 gram intravenous infusion hourly was used despite the fact that Pumwani Maternity Hospital uses both the Zuspan and the Prichard regimens. This was mainly to standardize the dose for comparison purposes . After the loading dose, serum magnesium levels were determined and of the total study population, 101(59.4%) had subtherapeutic levels and 69(40.6%) had therapeutic levels. Follow – up levels at 4 hours and at 24 hours showed a decrease in the proportion of patients having subtherapeutic levels . After 4 hours the proportion having subtherapeutic levels had decreased to 55.3% and the mean serum magnesium level had risen to 1.93 mmol/L from the initial 1.85 mmol/L. After 24 hours of follow-up the proportion of patients with subtherapeutic levels had fallen to 48.1% and the mean serum magnesium level at this time was 1.98 mmol/L. This was probably because of the additional bolus magnesium sulphate doses of 2 to 4 grams that were administered if the patient convulsed while on therapy.

There was occurrence of convulsions while on magnesium sulphate therapy in 18.8% of patients in this study. This is higher than the rate of occurrence of convulsions generally reported as 10 – 15% in other texts [2,13]. This is probably because this other studies were done in North America where higher dose regimens are used: - of a loading dose of 6 grams and maintenance of 2 gram hourly is used [13, 15]. The rate of convulsions despite therapy found in this study is close to that found in the Eclampsia collaborative control trial group of 23.8% when the Zuspan regimen which is similar to that used in this study of 4 grams loading dose and a maintenance of 1 gram hourly was used [32]. In contrast for those patients for whom the Prichard regimen (Intramuscular regimen) was used, which gives a higher total dose of magnesium sulphate, the rate of recurrence was lower at 2.85% [32]. A retrospective study by Chege in KNH in 2004 reported a 9.7% occurrence of convulsions while on magnesium sulphate[4]. The rate found in this study is double (18.8%) that found in his study which could be of possible higher pick up rate this being a prospective study. In this study group 2 (2.6%) patients out of 76 patients

with severe preeclampsia had convulsions despite therapy. In the magpie collaborative trial group the rate of convulsions for patients with severe preeclampsia receiving magnesium sulphate was much lower (0.8%). This could be because of the greater power in the magpie study compared to this study[5].

The study shows a high correlation between the serum magnesium levels and the body mass index of the study population. The body mass index was inversely proportional to the serum magnesium levels and the two were highly correlated($p<0.05$). The odds of subtherapeutic serum magnesium levels with a high BMI (Overweight or more) was 86.5 times that for those patients with a normal BMI ( 95% CI 13.6-355.5 , $p = 0.001$). In a study by Dayaciglou, the serum magnesium levels were inversely related to the BMI and those patients with BMI s above 30 had subtherapeutic levels of serum magnesium [18]. In this study the mean body mass index was 28 with majority (67%) of the patients having a body mass index of 25 and above. In study by Ekele in Nigeria of 19 patients, the mean body mass index was 21.9 and the mean serum magnesium level was 1.95 mmol/L after the loading dose [19]. In low dose regimens studied in India by Sardesai and Begam, where patients had an average weight of 48 kilograms, therapeutic serum magnesium levels were still achieved in a majority of the patients when half the total dosage of magnesium sulphate used in the Prichard regime was used for these patients.

There was a significant association between subtherapeutic levels of serum magnesium and failure of to control convulsions. Of the patients who convulsed while on the standard dose of magnesium sulphate regimen used, 78.1% were in the subtherapeutic category while 21.9% who were in the therapeutic group. The odds for convulsions for patients with subtherapeutic serum magnesium levels was 2.91 that for those patients with therapeutic serum magnesium levels ( 95% CI 1.10 to 7.98, $p = 0.016$). In the study by Sibai 11(84%) of the 13 patients who convulsed were found to have subtherapeutic levels while receiving a similar dose regimen of magnesium sulphate in this study[15]. In the other studies by Aali and Dayaciglou, failure of control of convulsions was not significantly associated with subtherapeutic levels possibly because the numbers of patients studied in the two studies were quite small. In this study and in the study by

Sibai, convulsions were controlled by addition of a bolus dose pointing to the fact that a higher serum levels are associated with better control of convulsions. In the patients studied there were no toxic levels (>3.5 mmol/L) of serum magnesium found.

Severe proteinuria (3+ and 4+) was associated with a higher chance of failure to control convulsions. The odds for failing to control convulsions for patients with elevated proteinuria (3+ and 4+) is 2.41 that for those with lower proteinuria levels of 2+ and less ( 95% CI 0.97 to 6.10, p = 0.013). None of the other studies showed a significant correlation between the proteinuria level and the failure to control convulsions with a standard dose of magnesium sulphate. As in other studies the severity of hypertension and the pregnancy status (antepartum, intrapartum or postpartum) was not significantly associated with the failure to control convulsions[15,20]. In the study despite the fact that a large number of those who convulsed while on therapy were primigravida (31%) and were less than 24 years old(46%), there was no significant association between parity and age and failure to control convulsions.

**Conclusions**

The use of the standard dose regimen of magnesium sulphate of 4 grams loading dose and 1 gram hourly maintenance failed to give therapeutic levels of serum magnesium in a majority of patients in 24 hours.

Many of the patients who had convulsions while on treatment with magnesium levels had subtherapeutic serum magnesium levels.

A high body mass index in the patients was associated with a higher frequency of subtherapeutic levels

**Recommendations**

It has been demonstrated by this study that the standard dose of serum magnesium fails to give therapeutic levels in majority of patients. A dosage formulation that possibly uses the body mass index where available could be formulated to give more uniform levels.

Randomised clinical trials should be designed comparing the higher dose regimens used in other areas of the world with the lower dose regimen used here.

Larger studies to determine the body mass index characteristics of our populations should be done .

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## APPENDIX

**CONSENT FORM**

To be filled by patient or relative of patient (if patient not able to consent)

**CONSENT FORM** **Date: ___/___/_____**

**Consent to participate in a study on determination of serum magnesium levels in patients treated with $MgSO_4$ for eclampsia/severe pre-eclampsia**

Dear Patient,

Due to the hypertensive complications you have, a decision has been made to administer to you a drug that will prevent convulsions from occurring or recurring. This drug is called Magnesium sulphate and has been shown to prevent and control convulsions that occur in this condition. The convulsions need to be controlled because they would adversely affect you and your baby. The drug has been used for many years and we have ways of checking so that it does not affect you adversely. The drug would still have been used even if you were not participating in this study

We are carrying out this study to see whether this drug achieves the required levels in the blood to control these convulsions and whether there are any other effects associated with the drug administration. We will not interfere with your care or adjust the dose of the drug in any way but will observe you carefully and also draw blood samples twice in addition to the routine ones that would have been drawn. We are going to do periodic examinations on you as would have happened even if you were not involved in the study.

You are invited to take part in the study but if you feel reluctant please say so and you will still receive the best of care as is usual. If at any time of the process you feel unwilling to continue being in the study please say so and be assured that at no time will pressure to participate be put on you. If you have any questions at any time about the study and procedure please feel free to ask.

If you are willing to participate please sign the form on next page.

Declaration

***Investigators statement***

I have explained to the respondent the nature and purpose of the study as described above. I have asked the subject if there are any further questions and I have answered them to the best of my knowledge and ability.

Signature of Investigator .....

***Interviewee's statement***

I have understood the nature and purpose of this study and hereby voluntarily consent to participate.

**Patient's signature or thumb print.....**

**Name of patient printed.....**

**Witness**

Signature.....Name.....

**Contact**: Dr. Jane Machira, P.O Box 6817 00100 Nairobi tel no. **0722659399**

Name of other persons who can be contacted to answer questions that patients may have are:

Prof. Muia Ndavi
Associate Professor, Department Of Obstetrics and Gynaecology
University of Nairobi

Dr. Barbara Magoha
Specialist Obstetrician/Gynecology, University Health Services
Honorary Lecturer Department of Obstetrics and Gynecology
University of Nairobi

**Note :**

Relative:– Close blood relative eg. mother, father, spouse and sibling

Relatives consent to be sought only if patient comatose or not well oriented in time, space or person.

## DATA COLLECTION FORM

**Demographic Data**

1. Location A) **K.N.H** [ ] B)**P.M.H** [ ]
2. Study No _____
3. Hospital No_____
4. Time of admission (24 hour clock) __ __:__ __ Date __ __/__ __/__ __
5. Age in Years(completed) _____
6. Parity _____ + _____
7. Gestation in completed weeks _____ Lmp __ __/__ __/__ ___
8. Height _____Meters
9. Weight _____(Kilograms)
10. BMI (calculated from above) Kilograms/Meters$^2$ _____
11. Occupation _____
12. Marital status (tick) Single [ ] Married [ ] Separated /divorced [ ] widowed [ ]
13. Educational level(tick)

    None [ ] Primary school [ ] Secondary school [ ] College [ ] University [ ]

14. Blood pressure at admission _____ / _____mm Hg
15. Temperature __.__ °C
16. Blood slide for malaria : Mps present Yes [ ] No [ ]
17. Random Blood sugar __.__ mmol/l
18. Proteinuria ____ +

**Eclampsia**

19. No of convulsions before drug administration _____
20. Patient Not in labour [ ] In labour [ ] Post delivery [ ]
21. If post delivery , how long ago ____days ____hrs

**Severe Pre-eclampsia**

22. Presence of the following

    a)Severe headaches [ ] b)Thrombocytopenia [ ]

    c) Blurring of vision [ ] d) Deranged liver-enzymes [ ]

o) Epigastric pains [ ]

## $MgSO_4$ ADMINISTRATION

23. Magnesium loading dose

a. Dose _____ Gms b. Time of administration ____:____(24 hrs)

24. Maintenance dose _____gms /hour

25. Supplemental $MgSO_4$ dose (incase of continued convulsions)? **Yes[ ]** **No[ ]**

If [Yes] note the dose and the hour in the table next page:

| Hour | TIME | $MgSO_4$ | Additional MgS04 |
|---|---|---|---|
| 1 | _ _:_ _ | Loading dose [ ] _ _ gms I.V | [ ] _ _ gms |
| 2 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 3 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 4 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 5 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 6 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 7 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 8 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 9 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 10 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 11 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 12 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 13 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 14 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 15 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 16 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 17 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 18 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 19 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 20 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 21 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 22 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |

| | | | |
|---|---|---|---|
| 23 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |
| 24 | _ _:_ _ | Maintenance dose _ _gms I.V | [ ] _ _ gms |

**LABORATORY VALUES**

26. Serum Magnesium levels

    a. Sample 1 (30 minutes after loading dose) _____mmol/L

    b. Sample 2( 4 hours after first dose, during maintenance)_____mmol/L

    c. Sample 3(24 hours, after completion of MgSO4 infusion)_____mmol/L

27. Serum Creatinine level _____mmol/l (30 minutes after loading dose)

**CLINICAL DATA**

28. If convulsions recur during treatment with $MgSO_4$, note the time in the table below and tick in the convulsions column

29. Record the respiratory rate / minute every hour

30. Note the state of the Patella reflexes below ( presence or absence)

| Hour | TIME | Convulsions (Tick) | Respiratory rate/min | Reflexes + or - | Urine output (Mls) |
|---|---|---|---|---|---|
| 1 | _ _:_ _ | | | | |
| 2 | _ _:_ _ | | | | |
| 3 | _ _:_ _ | | | | |
| 4 | _ _:_ _ | | | | |
| 5 | _ _:_ _ | | | | |
| 6 | _ _:_ _ | | | | |
| 7 | _ _:_ _ | | | | |
| 8 | _ _:_ _ | | | | |
| 9 | _ _:_ _ | | | | |
| 10 | _ _:_ _ | | | | |
| 11 | _ _:_ _ | | | | |
| 12 | _ _:_ _ | | | | |
| 13 | _ _:_ _ | | | | |
| 14 | _ _:_ _ | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 15 | _ _:_ _ | | | | |
| 16 | _ _:_ _ | | | | |
| 17 | _ _:_ _ | | | | |
| 18 | _ _:_ _ | | | | |
| 19 | _ _:_ _ | | | | |
| 20 | _ _:_ _ | | | | |
| 21 | _ _:_ _ | | | | |
| 22 | _ _:_ _ | | | | |
| 23 | _ _:_ _ | | | | |
| 24 | _ _:_ _ | | | | |

# Ethical Approval Letter

**KENYATTA NATIONAL HOSPITAL**
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Ref: KNH-ERC/ 01/ 403

20th May, 2008

Dr. Machira Jane
Dept. of Obs. & Gynae
UNIVERSITY OF NAIROBI

Dear Dr. Machira

**RESEARCH PROPOSAL: "SERUM MAGNESIUM LEVELS AND THERAPEUTIC OUTCOMES IN PATIENTS TREATED WITH MAGNESIUM SULPHATE FOR ECLAMPSIA/SEVERE PRE-ECLAMPSIA IN KENYATTA NATIONAL HOSPITAL AND PUMWANI MATERNITY HOSPITAL" (P51/3/2008)**

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 20th May, 2008 – 19th May, 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

**PROF A N GUANTAI**
**SECRETARY, KNH-ERC**

c.c. Prof. K.M. Bhatt, Chairperson. KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UoN
The Chairman, Dept. of Obs. & Gynae, UoN
Supervisors: Prof. Muia Ndavi, Dept. of Obs.& Gynae, UoN
Dr. Barbara Magoha, Dept. of Obs. & Gynae, UoN

**Intravenous Magnesium Sulphate Regimen used at Kenyatta National and Pumwani Maternity Hospital in treatment of Eclampsia and Severe Preeclampsia.**

***Loading dose***

⇒ Give 4g of 20% magnesium sulphate solution IV over 15 to 20 minutes

⇒ If Convulsions recur after 15 minutes give 2g -4g of magnesium sulphate over 15 to 20 minutes

***Maintenance dose***

Give 1 gram of 20% magnesium sulphate solution in a continuous infusion for 24 hours after last convulsion or after delivery.

**Closely monitor the woman for signs of toxicity**

Before repeat administration, ensure that:

⇒ Respiratory rate is at least 16 per minute

⇒ Patellar reflexes are present

⇒ Urinary output is at least 30ml per hour over four hours

Keep antidote ready.

In case of respiratory arrest:

- Assist ventilation
- Give calcium gluconate I gram (10mls of 10% solution) IV slowly until respiration begins