Eclampsia: A randomized double blind trial of magnesium sulphate and Diazepam in Lagos, Nigeria

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Abstract

Background: Magnesium sulphate is used widely to prevent eclamptic seizure in pregnant women with Hypertension but few studies have compared the efficacy of magnesium sulphate with that of other drugs in Nigeria.
Objective: This randomnized study is to compare the efficacy of magnesium sulphate with that of diazepam in preventing seizures in hypertensive women during labour.
Methods: Eclamptic patients were randomly assigned to receive either magnesium sulphate or diazepam. The magnesium sulphate regimen used was as described by Zuspan. The diazepam regimen was a loading dose of 10mg intravenously over two minutes and repeated when convulsions recurred.
Primary measure of outcome: Recurrence of convulsions and maternal death.
Results: The use of magnesium sulphate was found to be significantly associated with less serious morbidity in terms of recurrence of convulsions (P = 0.0047), respiratory, and renal complications (P = 0.004) and improvement in level of unconsciousness (P = 0.0024) in comparison to diazepam use. Eight maternal deaths occurred, seven (87.5%) in unbooked/ predelivery patients. More vaginal delivery and less operative delivery were recorded in the magnesium group as compared to the diazepam group (P = 0.039). Low Apgar scores < 7 at 1min were twice as common in the diazepam group as compared to the magnesium sulphate group (P = 0.04). There were four early neonatal deaths in the diazepam group and none in the magnesium sulphate group.
Conclusion: This study has produced support for the touted advantages of magnesium sulphate over diazepam for the mother and the infant in the treatment of eclampsia.

Key Words: Eclampsia, Recurrent Convulsions, Magnesium sulphate,Diazepam [Trop J Obstet Gynaecol, 2004; 21:143-147]

Introduction

Eclampsia is still one of the leading causes of maternal mortality[1] and continues to be a significant cause of serious maternal morbidity all over the world[1, 2]. Eclampsia is said to complicate 1 in 2000 deliveries in Europe and other developed world[2], while in developing countries estimates vary widely, from 1 in 100 to 1 in 1700[3]. The attending maternal mortality is reported as 0 to 20% and perinatal mortality between 10 to 28%[4]. Although mortality is frequently reviewed, morbidity (maternal or fetal) is rarely mentioned[5]. This is unfortunate because even the surviving infants are in jeopardy of life long handicaps with adverse social and economic consequences.[6]

The present management of eclampsia aims to stop the convulsions and prevent recurrence, control the blood pressure, correct fluid and electrolyte imbalance and deliver the patient promptly. The anticonvulsants and antihypertensive therapy should protect the woman and her fetus from deleterious effects of convulsion, but should not expose either to additional risks from the therapy. However the choice of the most effective anticonvulsant is controversial. Currently the most widely used anticonvulsants are magnesium sulphate, diazepam and phenytoin sodium and excellent results of varying degrees and with different side effects have been reported[7].

In our hospital, the anticonvulsant of choice for the last one and half decade in the management of eclamptic fits is diazepam. This is found suitable as reported by other developing countries because it is inexpensive, readily available and easy to administer. Prior to this, we had used Rectal bromethol (1967 69), lytic cocktail (1969 72) 0.8% Heminevrin (Chlormethazole)- 1972 1986, at different periods and the various experiences had been reported elsewhere[8].

Despite the various evidence in favour of magnesium sulphate about its effectiveness and safety in management of eclamptic fits, [7] it has not been used in our hospital. This randomized comparative and blind clinical trial was to evaluate the efficacy of magnesium sulphate and Diazepam in the treatment and prevention of eclamptic seizures and also to define a clear relationship between their use and their relationship to the maternal and perinatal morbidity and mortality in our institution.

Materials and Methods

This prospective comparative randomized study was carried out in the Obstetrics and Gynaecology Department of the Lagos University Teaching Hospital LUTH), Lagos, Nigeria. Eclamptic patients that

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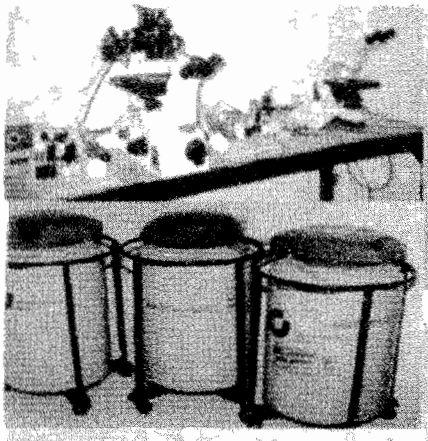

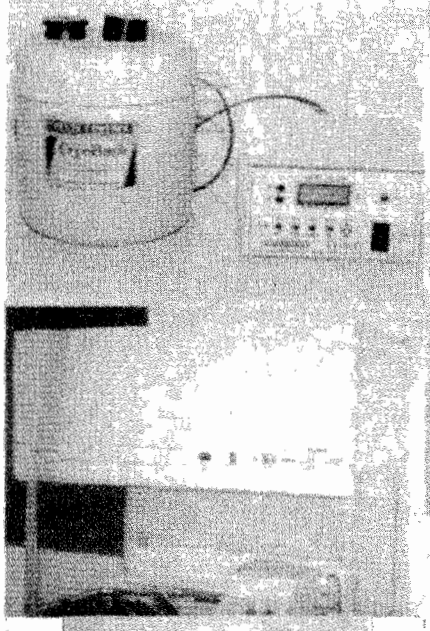

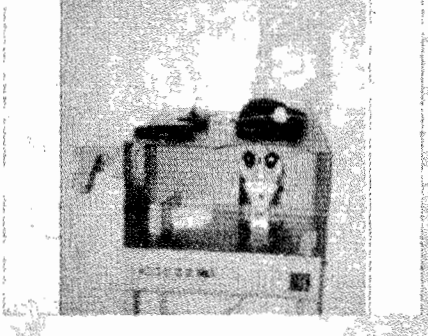

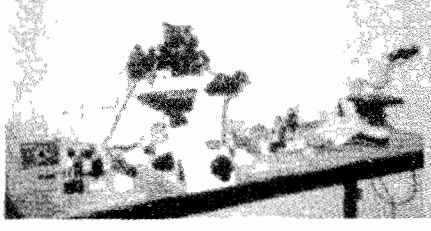

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satisfied the eligibility criteria were randomly allocated to either magnesium sulphate ($MgSO_4$) or diazepam regimen using computer generated randomized numbers. Eligibility criteria were based on occurrence of convulsion during pregnancy or within 10 days post partum with the following features within 24 hours after the convulsion or before onset of convulsion: (a) Hypertension with a level $\geq$ 140/90 mmHg (b) Protenuria at least (1^+) dectected on Urine dip stick using catheter specimen of urine. The minimum sample size was based on the prevalence of eclampsia at LUTH using the formula $n = Z^2\ pq/\ d^2$ where n is minimum sample size required for the study, Z is 1.96 at 95%. Confidence levels q is 1-p, d is acceptable error margin of 5% at 95% confidence level. P is prevalence of eclampsia at LUTH. The equation gave the minimum sample size to be approximately 18. A sample size of 60 patients which was higher than the minimum sample size of 18 was used for this study, and comprising of 30 patients for each trial group which is still above the minimum size of 18.

Women were allocated to an anticonvulsant regimen in sealed treatment packs marked A or B. A computer generated randomized number was used to assign patient to A or B. The sealed treatment packs were identical in size, shape, weight and feel. All packs contained sufficient anticonvulsant for the loading dose and for 24 hours maintenance therapy and treatment of one recurrent convulsion. Magnesium sulphate packs also contained 1g calcium gluconate in case of magnesium toxicity. To enlist a woman into the trial, the data form was completed including the date, time, patients name and hospital number, parity, gestational age, booking status, blood pressure and whether the baby had been delivered. The pack was then opened and allocated anticonvulsant administered.

For magnesium sulphate therapy, the continuous intravenous regimen was as described by Zuspan[9] was used. For diazepam therapy, a loading dose of 10mg intravenous over 2 minutes was administered and repeated when convulsion recurred. Subsequently, 10mg diazepam injection was administered intravenously every 6 hours to keep the patient sedated but rousable for the next 24 hours. The subsequent dose was omitted when the patient was still sedated at the time it was due.

The primary measures of outcome were recurrence of convulsions and maternal death. The secondary measures were potentially life threatening events, including pulmonary edema, cardiac arrest, respiratory depression, aspiration pneumonitis, renal failure, disseminated intravascular coagulation, cerebrovascular accidents, liver failure, post-partum hemorrhage and Glassgow Coma Scale score (GCSS) on admission and 24 hours after commencement of treatment. Mental status was frequently measured objectively using the Glasgow Coma Scale[10], which takes into account, on a graded scale, the patient's best eye opening, verbal and motor response. The mode of delivery, indications and blood loss at delivery were included.

For predelivery eclamptics, additional outcome measures included mode of delivery, Apgar scores and need for admission into neonatal unit for intensive care and perinatal deaths.

The data was analysed by computer using the Epi Info (version 6) software package. The student's t-test was used for the comparison of means of the quantitative variables while the chi-square test was used for the comparison of the proportions, and Fisher's exact test for low expected values. Where appropriate, relative risks and associated 95% confidence intervals were determined for the outcome measures. Differences were said to be statistically significant where the associated p-values were equal to, or less than 0.05 or, in the case of relative risks, where the confidence interval did not include a value of 1. The Excel graphics was used for graphical presentation.

Results

Sixty patients were studied equally distributed in the two groups (30 each). Thirty-two patients (53.3%) were nulliparas while the rest 43.7% were multiparous. The mean age of the patients in the magnesium sulphate group was 25.6 ± 4.94 (SD) years and diazepam group 27.4 ± 5.53 (SD) years. In all, only 22 patients (36.6%) were less than 25 years of age. There were no statistical difference in parity and age distribution in the two groups ($p > 0.543$ & 0.369). Majority of the patient 54 (90%) had one form of prenatal care elsewhere and only 6 (10%) occurred in patients that had prenatal care in LUTH. History of pregnancy-induced hypertension/eclampsia in previous pregnancies was obtained in 11 (18.4%) of the patients while 17 (28.4%) of the patient had PIH in the index pregnancy, while no significant history in 53.3%. Fifteen patients (25%) had delivered before occurrence of fits, while 22 patients (36.8%) were intrapartum and 23 patients (38.3%) were antepartum. Seventy-three percent of the patients had more than two episodes of fits before trial entry. Also, at trial entry 57.8% of the patients were pre-term pregnancy, 60% of the patient had diastolic blood pressure of 110mmHg or more, 56.7% had systolic blood pressure of 170mmHg or more, 81.7% of patients had proteinuria of 2+ or more. None of these factors were of statistical difference in the two groups. (Table I)

Eight maternal deaths occurred in the entire cohort of patients. Disseminated intravascular coagalopathy accounted for half of the deaths; others were as shown in Table 2. Among the women allocated to magnesium sulphate the maternal mortality was found not to be significantly lower 3(10%) as compared to 5(13.7%) among the diazepam group. Most (87.5%) of the deaths

Table 1: Characteristics Of Eclamptic Women At Trial Entry

Parity	$MgSo_4$	(No. %)	Diazepam	TOTAL (n=60) (No. %)	Statistical Significance
Primiparous	15	(50%)	17 (57%)	32 (53.3%)	
Multiparous(1-5)	15	(50%)	13 (33%)	28 (46.7%)	P = 0.543 NS
Age(in yrs)					
15 19	2	(6.7%)	Nil	20 (3.3%)	
20 34	22	(73.3%)	27 (90%)	49	
≥35	6	(20%)	3 (10%)	9 ((15%)	P = 0.369 NS
MEDICAL HISTORY					
PIH in index Pregnancy/ Imminent Eclampsia	9	(30%)	8 (26.7%)	17 (28.4%)	P=0.736 NS
Previous History of Preeclampsia/ Eclampsia	5	(16.7%)	6(20%)	11 (18.4%)	
No Significant History	16	(53.3%)	16 (53.3%)	32 (53.3%)	
Type of Eclampsia					
Antepartum	10	(33.3%)	13 (43.3%)	23 (38.3%)	
Intrapartum	12	(40.0%)	10 (33.3%)	22 (36.8%)	
PostPartum	8	(26.7%)	7 (23.3%)	15 (25%)	P = 0.765 NS
Gestational Age Intra/Antepartum Eclampsia					
≥37 week(term)	4	(8.9%)	12 (26.7%)	16 (35.6%)	
32 36 weeks	12	(26.7%)	6 (13.3%)	18 (40%)	
≤32 weeks	5	(11.1%)	3 (6.7%)	8 (17.8%)	P=0.078 NS
Uncertain dates	1	(2.2%)	2 (4.4%)	3 (6.7%)	
Total	22	(48.9%)	23 (51.1%)	45 (100)	
PostPartum Eclampsia					
> 37 weeks	6	(40%)	5 (33.3%)	11 (73.3%)	
32-36	Nil	(-)	Nil (-)	(-)	
< 32	Nil	(-)	Nil	(-)	
Not known	2	(13.3%)	2 (13.3%)	4 (26.6%)	
Total	8	(53.3%)	(46.6%)	15(100%)	
Fits before Trial Entry					
1	4	(13.3)	10(33.3)	14(23.3)	
2-5	19	(63.3)	15(50)	34(56.7)	
> 5 6	(20)		4(3.3)	10(16.7	P=0.328 (NS)
Not known	1	(3.3)	1(3.3)	2(3.3)	
B.P AT ENTRY					
Diastolic B.P. > 110mmHg	16	3.85	18	60	
Systolic B.P. > 170mmHg	18	(56.7)	60	17	
PROTEINURIA AT ENTRY					
1+	5	(16.7)	3 (10)	8 (13.3)	
2+	6	(20)	9 (30)	15 (25)	
3+	19	(63.3)	15 (50)	34(56.7)	P=0.206NS
Not known*	Nil	(-)	3 (10)	3 (5)	

Were in the unbooked patients and in the pre-delivery ecalmptic patients.

The rate of recurrence of convulsions among magnesium sulphate subject was found to be significantly lower three patients (10.7%) as compared to thirteen patients 50% in the diazepam subjects (P = 0.0047) Table 2. Four cases in the diazepam group had uncontrolled convulsions and had to be "crossed over" to the magnesium sulphate group.

In the women allocated to magnesium sulphate less serious maternal morbidity were recorded as compared to the diazepam group as shown in table 3 i.e. Aspiration Pneumonia 0(0%) vs 7(23.3%), Renal failure 2(6.7%) vs 9(30%), cardiac arrest 0(0%) vs 3(10%). These difference were reflected in the overall outcome as 22(73.3%) of the magnesium sulphate group had no complications compared to only 1(3.3%) in the diazepam group. This difference was found to be statistically significant (P=0.001).

Table 2: Primary Measures Of Outcome Maternal Death, Causes And Entry Characteristics.

A. Maternal deaths	*$MgSo_4$*	*(%)*	*Diazepam*	*(%)*	*Total*	*(%)*
Causes of Death	*n-3*	*%*	*n-5*	*%*	*n =8*	*%*
Disseminated Coagulopathy	2	25	2	25	4	50
Post -Partum Haemorrhage	1	12.5	Nil	-	1	12.5
Anaesthesia	Nil	½		12.5	1	12.5
Aspiration pneumonia	Nil	½		12.5	1	12.5
Acute renal failure	Nil	½		12.5	1	12.5
Entry Characteristic						
Pre -Delivery Eclampsia	3	37.5	4	50	7	87.5
Post -Partum	Nil	-	1	12.5	1	12.5
Booking Status						
Booked	1	12.5	Nil	Nil	1	12.5
Unbooked	2	37.5	5	50	7	87.5
Parity						
Multipara	3	37.5	3	37.5	6	75
Nulli para	Nil	Nil	2	25	2	25
Gestational age						
Preterm (< 36 weeks)	3	37.5	2	25	5	62.5
Term (> 37 weeks)	Nil	Nil	3	37.5	3	37.5
Blood Pressure						
DBP > 110mmHg	3	37.5	3	37.5	6	75
DBP < 110mmHg	Nil	Nil	2	25	2	25
Proteinuria						
++	2	25	2	25	4	50
+	1	12.5	1	12.5	2	25
Not Done						
GCSS Scale	Nil	Nil	2	25	2	25
GCSS < 8 after 24 hours	1	12.5	5	62.5	6	75
GCSS > 8 after 24 hours	2	250	Nil	Nil	2	25
B. Recurrence of fits	n = 28	%	n = 26	%	n=54	%
Recurrence of Fits						
Fits Recurring 1-2	3	(10.7)	9	(34.6)	12	(23)
Fits Uncontrolled by Anticonvulsant (> 2)	Nil	Nil	4	(15.4)	4	(7.2)
Nil further Fits	25	(89.3)	13	(50)	38	(70.0)
TOTAL	28	(100)	26	(100)	54	(100)

Eighty percent of the patients allocated to magnesium sulphate had improved glasgow coma scale score as compared to 36.7% patients on diazepam and also, no deterioration in level of consciousness in all patients allocated to magnesium sulphate group compared with 36.7 of patients in the diazepam group. These differences were statistically significant (P=0.0024).

In the pre-delivery ecalmptics, vaginal delivery was achieved in 60.5% of the patients while the rest had caesarean section. Significantly, vaginal delivery was more frequently achieved in the magnesium sulphate group (72.2%) as compared to (45.5%) of the diazepam group P=0.039. Four of the patients, in the magnesium sulphate group that delivered vaginally had postpartum

Table 3: Secondary Measures Of Outcome

PULMONARY EDEMA	MgSo4 n= 30 (%)		Diaze-pam n=30 (%)		Total (%)		P-Value
Present at admission*	1	3.3	2	6.7	3	5	0.5
Developed during+ treatment	Nil	Nil	Nil	-	-	5	1.00
ASPIRATION PNEUMONIA							
Present at admission*	3	10	5	16.7	8	13.3	0.353
Developed during + treatment	Nil	-	7	23.3	7	11.7	0.005 S
Cardiac Arrest +	Nil		3	10	3	5	0.119
Acute Renal Failure*	2	6.7	9	30	11	18.3	0.019 S
Disordered Coagulopathy*	2	6.7	2	6.7	4	6.7	1.00
Admission to I.C.U.	Nil	-	1	3.3	1	1.7	0.5
Nil Complication	22	73.3	1	3.3	23	38.3	0.001 S
TOTAL	**30**	**100**	**30**	**100**	**60**	**100**	

\+ - Developed after commencement of therapy

* - Present on admission.

S - Significant

GLASGOW COMA SCALE SCORE 24 HOURS After Treatment	MgSo4 N=30(%)		Diazepam n =30(%)		TOTAL	(%)
Improvement in GCSS	24	80	11	36.7	35	58.3
Deterioration in GCSS	Nil	Nil	11	36.7	11	18.3
No change in GCSS	2	6.7	4	13.3	6	10
GCSS not done	2	6.7	2	6.7	4	6.7
Patient died less than 2 hours	2	6.7	2	6.7	4	6.7
TOTAL	**30**	**100**	**30**	**100**	**60**	**100**

$X^2 = 16.50$, df = 4 P = 0.0024 (Significant).

Haemorrhage but none in the diazepam group (Table 4). Twenty perinatal deaths occurred fourteen of these were stillbirths including babies of women that died undelivered. Depressed Apgar scores (< 7) were 2 times more frequent in babies of diazepam patients (14 versus 7) compared with magnesium sulphate group. This finding was of statistical significance P = 0.04. There were four deaths in the neonatal units amongst live born infants admitted with asphyxia, all of which were from the diazepam group.

TABLE 4: Measures of Outcome Relevant to Women Randomized Before Delivery

Delivery	Mg S04 n=21 (%)		Diazepam n=22 (%)		Total n=43 (%)		P Value
Vaginal delivery	16	(76.2)	10	(45.5)	26	(60.5)	0.039 S
Caesarean Section	5	(23.8)	12	(54.5)	17	(39.5)	
Blood Loss> 500mls	4	(19)	Nil		4	(9.3)	
For all babies							
Perinatal mortality	9		9		18		
Stillbirth	9		5		14		
Early Neonatal death	Nil		4		4		
Died Undelivered	1		1		2		
Total death	10		10		20		
For Live births							
Apgar score ≤ 7(Total)	7		14		21		P = 0.04 S
Midderate Asphyxia(4-6)	6		5		11		
Severe asphyxia < 3	1		9		10		

S -Significant.

Discussion

All the patients received the allocated anticonvulsants except in four of the diazepam patients that had to be changed to magnesium sulphate due to failure to prevent recurrent convulsions. This study further supports the claims about the effectiveness of magnesium sulphate in terms of control and prevention of further fits, in eclamptic patients. Among the patients that received magnesium sulphate no further fits occurred in 89.3% of the patients after the initial dose and in the few left no further fits after the 2nd dose. Whereas in the diazepam group control was only achieved in 50% of the cases allocated. In 4 (15.4%) of the patients prevention of recurrence of fits was not achieved. This finding is similar to that of the collaborative trial group as they also found in the series that patients allocated to magnesium sulphate had significantly lower risk of recurrent convulsion than those allocated to diazepam. The recurrence rate of 50% after diazepam is considerably higher than the 26% reported by Crowther[11]. This may mean that, in our study, diazepam serum levels were inadequate or that the drug is not as effective in preventing further fits from occurring. Intravenous titration of drugs requires extral nursing vigilance, which is not always possible in a busy maternity unit in the developing world. Too little diazepam results in recurrence of convulsions, too much diazepam results in over-sedation and respiratory depression. Great care still needs to be exercised, however, so that correct dosages are given in the appropriate manner and to ensure that the follow-up protocol is adhered to[12].

Eclampsia continues to be a significant cause of serious morbidity and is still one of the leading causes of maternal mortality. However this study showed that complications after treatment are less likely to develop in patients treated with magnesium sulphate as compared to diazepam therapy. It was found that complications occurred only in 27% of the patients allocated to magnesium sulphate as compared to 97% in the diazepam group. Improvement in clinical state and Glasgow coma scale score was more than two times achieved in magnesium sulphate group as compared to diazepam and also chances of patients developing aspiration pneumonia and cardiac arrest after commencement of therapy is almost nil in the magnesium sulphate group. All these complications noted in the diazepam group might not be unconnected with the fact that diazepam causes heavy and prolonged sedation with loss of laryngeal reflexes and thus increasing the risk of aspiration and other respiratory problems[11]. The renal function was significantly better with magnesium sulphate group as fewer women developed renal failure after admission. The mode of action of magnesium sulphate is incompletely understood but the beneficial increase in renal and uterine blood flow had been reported in literature[13] and this may explain why renal complications were not

observed in the magnesium group.

The outcome of labour showed that more vaginal delivery and less operative delivery were recorded in the magnesium sulphate group as compared to the diazepam group. One of the contributory factors to the high operative delivery in the diazepam group is the occurrence of fetal distress which is one of the recognized side effects associated with diazepam as it is known to depress fetal respiration. However postpartum haemorrhage was noted to be recorded only in the magnesium sulphate group and none in the diazepam group. One of the detrimental effects reported in literature[14, 15] is that magnesium sulphate reduces uterine activity and this might predispose to uterine atony and thereby causing post partum haemorrhage. It needs to be stated that this complication can be minimized and or prevented if the third stage of labour is adequately supervised and actively managed. This finding is in contrast to report of Leveno et al[16] who reported that there was no clinical evidence that magnesium sulphate had any effect on the outcome of labour in his large cohort of randomized eclamptic women.

There were 8 maternal deaths recorded in this study, 3 in the magnesium sulphate group and 5 in the diazepam group. The risk of maternal and perinatal death is said to increase as the number of fit increases[11]. Poor control could have contributed to the number recorded in this group. Four of the deaths, two in each group, were due to disseminated intravascular coagulopathy. Worthy of note among the maternal deaths are the one in the magnesium sulphate group due to post partum haemorrhage and the two in the diazepam group due to respiratory complications. It is suggested that the depressive effect of diazepam on maternal respiration with associated risk of aspiration and the tocolytic effect of magnesium sulphate on the uterine musculature could account for these findings.

The perinatal outcome also appeared better in the magnesium sulphate group. About two times more of the infants in the diazepam group compared to magnesium sulphate group had depressed Apgar Score. There was less need for intubation at birth and fewer babies required admission to the neonatal intensive care unit in the magnesium sulphate group and this difference was statistically significant. Four of the babies in the diazepam group died in the neonatal ward of respiratory complications.

This study suggests that magnesium sulphate has advantages over diazepam both for the mother and the infant in the management of eclampsia. Similar observation was reported by Duley and Henderson-Smart (2003) [17] in the Cochrane review, they concluded that magnesium sulphate appears to be substantially more effective than diazepam for treatment of eclampsia. In addition, considering other trial reports especially the Eclampsia Trial Collaborative Group about the efficacy of magnesium sulphate then one can safely conclude that the drug is safe and the use in Nigeria be popularized in our Health Institutions. The safety of magnesium had been further confirmed by the Magpie[18] trial and it has been recommended as safe for use in developing countries.

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