SAFETY AND EFFICACY OF BOLUS ADMINISTRATION OF MAGNESIUM SULPHATE FOR PREECLAMPSIA

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Contributors:

Enaruna NO (Guarantor): Designed and directed original study, conceived and conducted the data analysis, interpreted the results, and drafted the manuscript.

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ABSTRACT

Context: Magnesium sulphate is currently the drug of choice in the prevention and treatment of eclampsia. On-going research is addressing its administration in terms of dosage, duration and safety.

Objective: We evaluated a modified method of magnesium sulphate administration with respect to safety, efficacy and maternofetal outcome.

Design, Setting And Subjects: This was a prospective cohort study conducted at the UBTH, Benin City with patients managed for severe preeclampsia between June and December, 2011. The Zuspan regimen was compared with a modified intravenous regimen in which magnesium maintenance therapy was given as 1g hourly bolus injection administered over 10 minutes. Both methods were evaluated for safety, efficacy and materno-fetal outcome.

Result: The mean age, parity, gestational age and body mass index were 28.09±5.5 years, 2.72±1.98, 36.67±3.54 weeks and 26.51±5.60 respectively. Both methods achieved therapeutic levels, but blood pressure control was better in the continuous group than the bolus group (27% vs 100%, P=0.000). Birth asphyxia occurred in 14.8% of the babies and was 3 times more in the continuous group (22% vs 7.5%; p=0.062). More babies in the bolus group were admitted to SCBU (54.1% vs 7.9%; p=0.000). There was no early neonatal death, and no maternal death in the first week of puerperium.

Conclusion: This study showed that hourly bolus intravenous administration of magnesium sulphate is comparable to continuous intravenous therapy in terms of safety and efficacy in the treatment of severe preeclampsia. A larger scale study is recommended to further confirm our findings.

Keywords: safety, efficacy, bolus magnesium

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INTRODUCTION

Preeclampsia remains a common cause of maternal and perinatal morbidity worldwide and a cause of mortality especially in the underprivileged populations. In Nigeria, it is one of the leading causes of maternal mortality and contributes significantly to perinatal morbidity and mortality[1-5]. Following the landmark reports of Magpie Trial and Eclampsia Trial Collaborative Groups, magnesium sulphate is now firmly established to be the drug of choice for the prevention and control of seizures in preeclampsia, resulting in more than 50% reduction in eclampsia risk[6-8]. As a corollary, deaths attributable to eclampsia will be significantly reduced by making magnesium sulphate widely available, accessible, affordable and acceptable.

The Pritchard[9] and Zuspan[10] regimens of magnesium sulphate therapy have been in practice for many years, and are considered the standard regimens but Sibai[11] has recommended a different regimen. Using any of the two standard protocols, the target serum therapeutic levels of magnesium are 2.0-3.5mEq/l[8], while Sibai uses plasma levels of 4.0-8.0mg/dl during treatment. Safe monitoring of the patients during treatment can be achieved using clinical tools including deep tendon reflexes, respiratory rate and urinary output. In their work, Ekele and Badung[12] found that the serum magnesium levels of eclamptic patients on treatment with magnesium sulphate did not exceed 3mmol/l, and thus concluded that routine estimation of serum magnesium was not necessary. While administering magnesium sulphate to treat severe preeclampsia and eclampsia in Kano State, Nigeria in 2008, the Population Council reported a toxicity rate of less than 2%[13]. It has been suggested that laboratory estimation be limited to cases where clinical monitors point to toxicity[12].

In the last decade, several authors have described various modifications to these regimens, emphasizing either the dose or duration of administration[14-16]. A method involving bolus administration of 2g every 2 hours was found to be inferior to the Zuspan regimen[17]. In the Department of Obstetrics and Gynaecology of University of Benin Teaching Hospital (UBTH), we have used a modification of Zuspan regimen in the last 5 years, with the maintenance given as bolus intravenous administration of 1g of 20% magnesium sulphate solution over 10 minutes every hour. This alternative scheme avoids the risks due to intramuscular magnesium sulphate and the difficult control with gravity-fed drip set, while allowing intravenous regimen in the absence of infusion pumps. The aim of this study was to assess the safety of this method and to compare the efficacy with that of the continuous intravenous regimen. The hypothesis that serum magnesium concentration and clinical efficacy of our modified regimen are similar to Zuspan's regimen was evaluated in this study.

MATERIALS AND METHODS

A prospective cohort study was conducted between June and December 2011 at the Obstetrics and Gynaecology Department of University of Benin Teaching Hospital (UBTH), Benin City with approval of the Institutional

Review Board. The subjects were patients treated with magnesium sulphate($MgSO_4$) for severe preeclampsia who were randomized to receive either bolus intravenous or continuous intravenous maintenance therapies. To achieve a uniform subject population, only patients with severe preeclampsia who booked in UBTH for antenatal care were included in this study. Postpartum cases of severe preeclampsia, patients with intrauterine fetal death, renal failure or those who had any treatment administered elsewhere before admission into UBTH were excluded.

Participants gave consent and were randomized equally using sealed brown envelopes containing labelled cards. Subjects randomized to group 'A' had the bolus protocol, while group 'B' had continuous intravenous regimen. Severe preeclampsia was defined as diastolic blood pressure (DBP) of ≥110mmHg and/or systolic blood pressure (SBP) of ≥ 160mmHg associated with proteinuria of at least 1+ on dipstick examination.

At admission, the patient was stabilized and preparation made for her delivery. Intravenous access was secured; blood was drawn for serum magnesium assay, electrolytes, urea and creatinine estimation, full blood count with platelets, liver function test and clotting time before commencing $MgSO_4$. Magnesium sulphate seizure prophylaxis was then commenced as outlined in the protocols with a bolus dose of 4g and maintenance dose of 1g/h; the modified treatment group had 1g of 20% solution given over 10min and repeated every hour for 24h, while the continuous intravenous group had the same 20% solution delivered at the rate of 1g/h as continuous infusion. An additional bolus intravenous dose of 2g was provided should there be seizure occurrence in both treatment groups. Treatment of acute rise in blood pressure was by intermittent slow intravenous administration of 10mg bolus hydrallazine for both groups, and was required whenever the DBP was 110mmHg or more.

Serum magnesium (Mg) level was monitored after 2h and thereafter, every 6h for the period of the maintenance treatment. Additional monitoring for magnesium toxicity was done with assessment for loss of deep tendon reflex, depressed respiration to less than 12 cycles/min, and reduced urinary output to less than 30 ml/hour, any of which necessitated withholding the next maintenance bolus dose in 'Group A' or stopping the magnesium sulphate infusion in 'Group B'. All the patients were monitored in the labour ward for 48 hours from admission inclusive of the period of the maintenance therapy which lasted for 24 hours, and their babies were followed up for one week.

The primary outcome measure was the comparison of serum magnesium levels achieved by both methods of magnesium sulphate administration, while secondary endpoint was to compare clinical outcome. Maternal clinical outcomes compared included level of seizure prophylaxis, loss of knee jerk reflex, respiratory depression, oliguria, number of deferred $MgSO_4$ doses. Neonatal outcome measures were stillbirth rate, Apgar scores, admission to special care baby unit (SCBU), requirement for calcium gluconate and early neonatal death (ENND).

In the determination of the sample size we assumed 58% reduction of eclampsia risk using the standard Zuspan regimen. Anticipating not more than 50% difference in the level of seizure prophylaxis with our current regimen, with a statistical power of 80%, confidence

interval of 90%, and the level of significance set at 0.05, a sample size of 50 patients in each group was obtained.

Five millilitres of venous blood was drawn for the estimation of serum magnesium before the loading dose of magnesium sulphate and then at 2 hours after the loading dose. Subsequently, Mg levels were done every 6 hours while the patient was on magnesium sulphate (just before the next due bolus dose of magnesium sulphate in treatment group 'A'). Another sample was required if the patient had seizure or showed signs of magnesium toxicity. Blood samples for Mg estimation were immediately transferred to the laboratory to be centrifuged after clot retraction to obtain serum. The separated serum was then used for the analysis or was frozen if analysis was not immediately possible. Analysis was done by standard techniques in the clinical chemistry laboratory using the kit by TECO DIAGNOSTICS, CALIFORNIA, USA[18].

The generated database was analyzed with a personal computer using the SPSS version 15 and GraphPad Instat 3. Categorical variables were expressed as absolute numbers and percentages and the differences in proportion between the two groups were analyzed using the Chi square test or Fisher exact test where appropriate, while continuous variables were presented as means with standard deviations and the differences between the two groups were analyzed with the Student *t* test. The level of significance was set as $p<0.05$

RESULTS

There were 100 patients included in this study, 50 in each treatment arm. The age range was 15 to 41 years, parity range was Para "0" to Para 5, and the gestational age range was 26 to 41 weeks. The mean age, parity, gestational age and body mass index were not significantly different between the two groups (Table 1). There were no cases of loss of knee jerk reflex, oliguria, deferred $MgSO_4$ doses, respiratory depression or episodes of seizure recorded in both treatment groups. There was also no maternal death in the study population.

The mean serum magnesium remained within the therapeutic range at all times of estimation except at the 2nd and 20th hours in the continuous intravenous group. Mean serum magnesium levels were similar in the two arms except at the 20th hour when the serum concentration of magnesium was 16% higher in the bolus intravenous group than the continuous intravenous group, though this difference was not statistically significant (2.30±1.01(SD) versus 1.98±0.85 mEq/L, p=0.09; Table 2). There was a gradual rise in the mean serum magnesium levels in both groups up to the 8th hour, and thereafter, a slow drop toward the 20th hour in the continuous intravenous group while a second peak was observed at this time in the bolus group (Table 2).

The mean DBP at admission for the two groups was similar; however, in the first 48 hours on admission, there was a significant difference in the requirement for hydrallazine to control DBP. Patients treated with bolus intravenous therapy were about 4 times more likely to require 4 or more doses of hydrallazine than the continuous intravenous group (100% versus 27%, p=0.000; Table 3). Hence, there was a better DBP control in the continuous intravenous therapy group. In both arms, DBP dropped significantly at the 6th hour with little change observed toward the 12th hour. After 12

hours of magnesium therapy, the mean DBP in the bolus group was 5% higher than that of the continuous group (95.5 versus 90.89mmHg; Figure 1). A secondary rise in DBP at the 18th hour was observed in both groups, though this change was more in the bolus intravenous group (5% versus 15%, p=0.0013; Figure 1).

The rate of stillbirth was the same in both groups. Birth asphyxia occurred in 12.0% of the babies and was 3 times more in the continuous group than the bolus group but this difference did not reach statistical significance (18% versus 6%, p=0.121; Table 4). However, the admission rate to SCBU did not reflect this difference in asphyxia rate as SCBU admission was 34% more in the bolus group than the continuous group (40% versus 6%, p=0.000). It is noteworthy that most of the babies were admitted because of prematurity and low birth weight (information not in table). There was no baby admitted to SCBU in both treatment arms who required calcium gluconate to treat clinical hypermagnesaemia. And none of the babies suffered early neonatal death.

DISCUSSION

The use of magnesium sulphate to treat severe preeclampsia has several advantages. It is known to reduce the risk of eclampsia by 58%[19] and also improves neonatal outcome, especially in preterm infants[20,21]. In particular, the use of magnesium sulphate reduces the risk of maternal death[13] by preventing eclampsia which is known to increase the mortality due to severe preeclampsia. And this study has shown that therapeutic levels of Mg can be achieved with both continuous and bolus intravenous schemes of magnesium sulphate administration, with comparable clinical outcomes for the mothers and babies in women with severe preeclampsia. The levels of seizure prophylaxis were the same for the two groups, though blood pressure control was better in subjects who had continuous intravenous scheme. There were no significant differences in the rate of stillbirth or birth asphyxia.

The sample size of this study is large when compared with previous works[12,17]. Again, one major advantage over some other studies is that only subjects with preeclampsia were recruited. Considering the peculiar pathogenesis of the disease and its progression, ensuring a homogenous study population was paramount in the conduct of this study. And the observed similarity in age, parity, body mass index and gestational age between the two groups further confirmed that the results obtained were likely reflective of our study variable, that is, the method of magnesium sulphate administration.

In order to capture the alterations in magnesium levels following the administration of the loading dose of magnesium sulphate, frequent collection of blood samples will be appropriate in the first hour, while hourly determination will be adequate subsequently to allow observation of changes to the magnesium level in subjects receiving bolus therapy. The timing of magnesium estimation in this study was aimed at observing the pattern of serum magnesium throughout the 24-hour period of treatment with magnesium sulphate which is different from the 4 hours studied by Abbade and co-workers[17].

Sibai and colleagues[22] showed that Pritchard regimen which combines intravenous and intramuscular injection of magnesium sulphate was a better way to achieve therapeutic levels of magnesium as well as maintain a plateau than Zuspan scheme which recommends

1g per hour as continuous intravenous infusion. However, Sibai's modified continuous intravenous regimen of 2g per hour was shown to achieve similar serum Mg levels as the Pritchard regimen after 3 hours of therapy. Abbade and co-workers[17] compared Zuspan scheme with a bolus intravenous scheme administered as 2g over 15 to 20 minutes every 2 hours. Peak serum levels were detected at 15 minutes in both groups; however, serum levels were significantly higher, plateau was maintained better and area under the curve was significantly higher in the Zuspan scheme than their alternate scheme. In another study, Ekele and Badung[12] demonstrated that therapeutic levels were achieved with Pritchard regimen in 19 eclamptic patients in whom they recorded a repeat seizure rate of 5%.

In this study, the pattern of serum magnesium observed during therapy showed that this bolus scheme is similar to the continuous intravenous regimen in achieving therapeutic levels. This is different from the report of Abbade and co-workers, and may be explained by the frequency of administration employed in our study as hourly versus every 2 hours in the former. The higher mean serum magnesium level at the 2nd and 20th-hour assays in the bolus therapy group is likely as a result of the high levels of magnesium achieved within 30 minutes of a bolus dose of magnesium sulphate[23]. The clinical implication of the 20th-hour secondary rise in serum magnesium level in the bolus therapy group is not immediately apparent but may be related to cardiovascular changes in the postpartum period.

Prior to and during the period of this study, patients with acute rise in blood pressure were treated with intravenous hydrallazine (we have routinely use labetalol). The patients who had bolus therapy had significantly more doses of hydrallazine for the control of blood pressure. It is likely that the steady maintenance of magnesium level in the serum by continuous therapy was associated with fewer requirements for hydrallazine. This may be explained by the antihypertensive role suggested for magnesium sulphate by the relaxation of smooth muscle which might have been more sustained in the continuous therapy group.

Similarly, the continuous therapy group was associated with faster reduction in diastolic blood pressure within the first 6 hours than the bolus group, but this finding was not statistically significant. In the same manner, subsequent blood pressure control was better in the continuous therapy group. In this study, a trend toward a secondary rise in diastolic blood pressure at the 18th hour was observed in both treatment groups, though this rise was also more in the bolus group. This may be explained by the rise in blood pressure that is known to occur after delivery and peaks at about the 3rd or 4th day[24].

This study revealed that the neonatal outcome was quite favourable when patients with severe preeclampsia are treated with magnesium sulphate. There have been reports of adverse neonatal outcome in babies exposed to magnesium sulphate in utero[25]. However, many recent studies seem to suggest a protective role for magnesium-exposed infants, especially when born preterm[20,21]. The favourable neonatal outcome may be explained by this effect as well as the favourable mean gestational age of 36.7 weeks at delivery. This effect was noted in the two treatment groups except for SCBU admission where the bolus therapy significantly contributed more babies to SCBU. Despite this difference in the admission rate there were no babies who suffered early neonatal death in both

groups.

It is instructive to note that stillbirth rate was similar in both treatment arms. The presence of stillbirth appeared to be due to the effect of the disease on the fetuses rather than the method of magnesium sulphate treatment. Severe preeclampsia has perinatal effects which may show as intrauterine growth restriction or intrauterine fetal death. This is especially so when the gestational age at delivery is remote from term. The mean gestational age of our study population was 36.7 weeks.

CONCLUSION

Magnesium sulphate remains an important drug for the treatment and prevention of eclampsia. Hourly bolus administration of magnesium sulphate is a useful alternative to the standard Zuspan protocol where infusion pumps are not readily available. A multicentre study designed to confirm the findings of this study, incorporating more frequent assessment of serum magnesium levels to further evaluate the utility of hourly bolus magnesium therapy in severe preeclampsia is recommended.

TABLES AND FIGURES

Table 1: Maternal socio-demographic characteristics

Characteristic		Frequency (%)		P-value
		Bolus (n=50)	Continuous (n=50)	
Age(years)	(28.09±5.5)	28.83±4.94	27.33±6.21	0.184
<20		6 (12.0%)	4(8.0%)	
20-29		23 (46.0%)	23 (46.0%)	
30-39		16 (32.0%)	17 (34.0%)	
=40		5 (10.0%)	6 (12.0%)	
Parity	(2.72±1.98)	2.73±1.87	2.71±2.03	0.959
0		26 (52.0%)	30 (60.0%)	
1-4		13 (26.0%)	11 (22.0%)	
=5		11 (22.0%)	9 (18.0%)	
Gestation(weeks)	(36.67±3.54)	36.19±3.51	37.16±3.48	0.168
<33		11 (22.0%)	13 (26.0%)	
33-36		14 (28.0%)	12 (24.0%)	
=37		25 (50.0%)	25 (50.0%)	
Body Mass Index(Kg/m^2)				
	(26.51±5.60)	26.42±5.51	26.56±5.68	0.901
Normal		22 (44%)	18 (36%)	
Overweight		24 (48%)	26 (52.0%)	
Obese		4 (8%)	6 (12.0%)	

Table 2: Maternal serum magnesium level in women treated with magnesium sulphate for preeclampsia

Time	Bolus (n=50)	Continuous (n=50)	T value	P value
0 h	1.82 ± 0.62	1.74 ± 0.77	0.572	0.569
2h	2.20 ± 0.55	1.89 ± 1.14	1.732	0.086
8h	2.42 ± 0.64	2.40 ± 2.11	0.064	0.949
14h	2.24 ± 1.18	2.16 ± 2.09	0.236	0.814
20h	2.30 ± 1.01	1.98 ± 0.85	1.714	0.089

Values are in milliequivalent per litre of serum and as mean ± SD

Table 3: Requirement for hydrallazine

		Number of hydrallazine in first 48 hours							Total
		1	2	3	4	8	10	14	
method of administration	Bolus	0	0	0	20	0	7	23	50
	Continuous	15	13	7	6	9	0	0	50
	Total	15	13	7	26	9	7	23	100

Table 4: Perinatal outcome following maternal treatment with magnesium sulphate for preeclampsia

Characteristic	Bolus dose group (n=50)	Continuous dose group (n=50)	P value
Still birth	3 (6.0%)	3 (6.0%)	1.322
Apgar score < 7 at 1 min	3 (6.0%)	9 (18.0%)	0.121
SCBU admission	20 (40.0%)	3 (6.0%)	0.000
Requirement for calcium gluconate	NIL	NIL	
Early neonatal death	NIL	NIL	

Abbreviation: SCBU, special care baby unit. Values are given as number (percent).

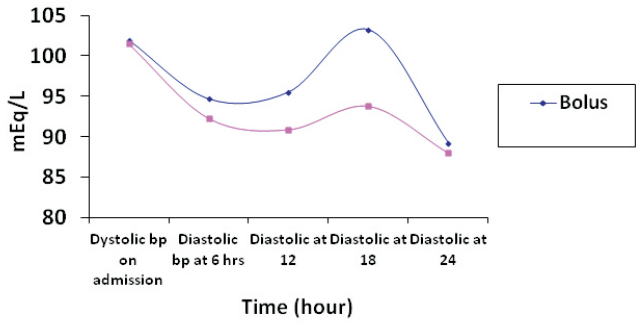

Fig. 1: Changes in diastolic blood pressure during treatment

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