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Comparison of Zuspan regimen and its 12-hour modification in women with severe pre-eclampsia and eclampsia in two hospitals in Abeokuta

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ABSTRACT

Background: Hypertensive disorders in pregnancy (HDP) are leading causes of maternal mortality (with severe pre-eclampsia/eclampsia [SPE/EC] being causes of death). Magnesium sulphate ($MgSO_4$) has proven to be the drug of choice for SPE/EC management. However, its availability and cost remain a drawback to its use in developing countries. This study aimed to compare Zuspan regimen with its 12-hour modification for SPE/EC management in two major hospitals in Abeokuta, Ogun state, South Western Nigeria.

Methods: A randomized controlled trial of non-inferior parallel design carried out at Federal Medical Centre and Sacred Heart Hospital, Abeokuta involving 148 consenting women who were randomized into two groups A and B. Both groups had 4 g loading dose of MgSO4, but the duration of maintenance was reduced to 12-hours in Group A (intervention) while Group B received the standard Zuspan regimen (control). Outcome measures were the occurrence/recurrence of convulsions (primary), maternal side effects and perinatal outcomes (secondary).

Results: There was no statistically significant difference in the occurrence/recurrence of seizures between the two groups for both SPE/EC. No signs of maternal toxicity were observed in both arm of the study. There were no statistically significant differences in the perinatal/neonatal death and Apgar scores at 1 and 5 min. However, there was a significant increase in the number of days on admission in the control group of those neonates delivered to mothers with eclampsia.

Conclusion: A 12-hr modification of Zuspan regimen was found to be non-inferior to the standard Zuspan regimen in the management of SPE/EC.

1. Introduction

Hypertensive disorders in pregnancy are leading causes of maternal and perinatal morbidity and mortality [1]. It complicates about 2–10% of pregnancies and accounts for 14.0% of maternal mortality globally [2–4]. The subsets; preeclampsia and eclampsia are mainly responsible for adverse maternal and perinatal outcomes accounting for about 9% of maternal deaths in Africa and Asia and about one-quarter of maternal deaths in Latin America and the Caribbean [3,4]. In Nigeria, eclampsia alone contributes to 12.4%−43.1% of maternal mortality [5–7].

Preeclampsia is a multi-systemic disorder characterised by development of hypertension with associated proteinuria, maternal organ dysfunction and/or placental dysfunction [8]. Eclampsia is the occurrence of generalized tonic-clonic convulsions in a woman with background pre-eclampsia in the absence of neurological, endocrinologic or metabolic derangements [9]. Eclampsia occurs in 1/43 – 1/41 (2.3 – 2.45%) deliveries in Nigeria, 7.4/10,000 deliveries in Japan and 2.7/10,000 in the United Kingdom [7,10–12]. It is a major cause of death in patients with hypertensive disorders of pregnancy [5].

Magnesium sulphate ($MgSO_4$) regimens have evolved over time with

Abbreviations: HDP, Hypertensive disorders in pregnancy; SPE, Severe Preeclampsia; EC, Eclampsia; $MgSO_4$, Magnesium Sulphate.

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the commonest being Zuspan and Pritchard regimens [13]. The Zuspan regimen involves a loading intravenous dose of 4 g given over 10 – 15mins followed by an intravenous infusion of 1 g per hour for 24 h [14]. In a study by Oguntunde *et al.* [15], the challenges with the use of $MgSO_4$ were facility-oriented (most facilities assessed had no $MgSO_4$ in store), provider oriented (there was inadequate staffing and less than half of the providers had ever been trained on the correct use of $MgSO_4$ and community/patient-oriented (misconception of the disease entity thus preventing prompt presentation for care was identified).

Imaralu et al in their study on clinical correlates of $MgSO_4$ revealed that using the Pritchard regimen, $MgSO_4$ levels peak at 8 h and thereafter decline with recorded seizures occurring within 4 h before the onset of maintenance dose [16]. The effect of reduction in the maintenance dose of the Zuspan regimen to 12 h in Eclampsia and severe preeclampsia by Anjum et al and Unwaha et al respectively revealed its efficacy and safety in the prevention of convulsions [17,18]. However, while Anjum and colleagues did not assess maternal adverse effects and perinatal outcomes, Unwaha et al did not assess the effect as regards postpartum haemorrhage [17,18].

This study thus aimed to compare the Zuspan regimen with its 12-hour modification in the treatment of severe pre-eclampsia and eclampsia (SPE/EC) at Federal Medical Centre and Sacred Heart Hospital, Abeokuta, Ogun state, Nigeria. The outcomes of interest include the occurrence of seizures, maternal signs of $MgSO_4$ toxicity including loss of deep tendon reflex, respiratory depression and pulmonary oedema, blood loss at delivery, Apgar scores, incidence of neonatal admissions and perinatal/neonatal deaths following treatment with the short course of $MgSO_4$ regimen as against the Zuspan Regimen in patients with SPE/EC.

2. Methods

This was a randomised double-blind placebo-controlled trial conducted at the departments of Obstetrics and Gynaecology, Federal Medical Centre and Sacred Heart Hospital, Abeokuta. The study involved two groups; Group A – intervention (4 g loading dose and maintenance dose for 12 h) and Group B– control (4 g loading dose and maintenance dose being standard for Zuspan Regimen).

Participants in this study included parturients with either severe preeclampsia or eclampsia at gestational ages of ≥34 weeks or in their puerperium but excluded those with urinary output less than 30mls/hr., those who had had previous administration of $MgSO_4$ or any form of anticonvulsants from the referral center, background history of seizures, metabolic disorders or other neurologic disorders, presence of other complications of SPE/EC including pulmonary edema and those with contraindication/ allergy to $MgSO_4$ (such as myasthenia gravis).

The sample size was calculated using the formula [19]:

$$N = 2x\left[\frac{z_{1-\alpha}+z_{1-\beta}}{\delta_0}\right]^2 xp(1-p)$$

$p = 5.7\%$ (rate of occurrence of convulsion (primary outcome variable) following treatment with $MgSO_4$ in the Collaborative Eclampsia trial) [20]; $\delta = 10\%$; $\alpha = 0.05$ thus $z_{1-\alpha} = 1.645$;$\beta = 0.20$ thus $z_{1-\beta} = 0.845$.

A total of 148 participants with 74 in each group were studied (using an attrition rate of 10%).

One hundred and forty-eight pre-packed study drugs which consisted of 74 packs of intervention drugs and 74 packs of control were provided. Using computer-generated '74' random numbers between 1 and 148, the number label for the intervention group (Group A) was determined and the remaining numbers were assigned to the control group (Group B). The 7 ampoules in the control packs contained 10mls of 50% w/v of $MgSO_4$ while the first four (I-IV) ampoules of the intervention packs comprised 10mls of 50% w/v of $MgSO_4$ and the last 3 ampoules were placebo (10mls of sterile water).

Patients were recruited into the study based on standard definitions of SPE/EC [8,9]. Randomization of the participants was based on the number labelled on the pack at the time of recruitment. Following randomization, 8mls was taken from **vial I** in a 20mls syringe mixed with 12mls of sterile water and this was administered as bolus intravenously over 15 mins. The remaining 2mls within the vial were discarded. Then, 8mls of contents of **vial II–VII** taken serially were then given as a continuous infusion in 500mls of 0.9% normal Saline alternating 5% Dextrose saline 4hourly.

Patients with recurrence of seizures had 2 g (4mls) $MgSO_4$ given to abort seizures if these occurred >30mins from the time of loading dose (Vial I). $MgSO_4$ for this purpose was of the same brand and batch but packed separately from the interventional medicinal products.

Information obtained from the participants through the proforma was coded and analyzed using the Statistical Package for Social Sciences (SPSS) version 25.

Ethical permission to carry out the study was obtained from both Hospitals' Health Research Ethics Committee (HREC). Protocol number was FMCA/243/HREC/03/2016/10; SHH/EC/EA/03/03/19. Written informed consent was obtained from each parturient before randomisation and those who declined to participate were managed according to the departmental protocol for such conditions without prejudice.

3. Results

All women recruited had allocated regimen and completed follow-up. The recruitment flow diagram is as shown in Fig. 1. Data analysis was done by intention to treat. Intervention group had 15 (20.3%) patients with eclampsia (EC) and 59 (79.7%) patients with severe pre-eclampsia (SPE) (with five (6.8%) post-partum EC and three (4.1%) post-partum SPE) while control group had 17 (23.0%) patients with EC and 57 (77.0%) with SPE (with three (4.1%) post-partum EC and seven (9.5%) post-partum SPE). Although fewer patients with EC were in the intervention than the control group, this difference was not statistically significant ($\chi^2 = 0.160$; $p = 0.690$).

Table 1 shows the Socio-demographic characteristics of the patients in each group. The modal parity for both groups was nulliparity. There was no statistical difference in both groups as per socio-demographics.

The modal urinalysis for Group A was 3+ of proteinuria while that for Group B was 2+ of proteinuria. No statistically significant difference occurred in the clinico-biochemical parameters between both groups as stated in Table 2.

Concerning patients with SPE, there was no statistical difference in the incidence of eclampsia and post-partum haemorrhage (PPH) between the two groups. The blood loss at delivery was significantly less in the intervention group than the control group (400mls (188) vs 500mls (200); $U = 1128.5$; $p = 0.044$).

There were no signs of $MgSO_4$ toxicity observed in both groups of parturient with SPE.

There were 56 (75.7%) participants with ante/intrapartum SPE in the intervention group and 50 (67.6%) with ante/intrapartum SPE in the control group. Of these, 40 (71.4%) participants in the intervention group and 37 (74%) participants in the control group had caesarean section but this difference was not statistically significant ($\chi^2 = 0.088$; $p = 0.829$).

There was no statistical difference in the recurrence of seizures between both groups of parturient with EC. There was no record of post-partum haemorrhage in both groups. The blood loss at delivery was significantly more in the intervention group than the control group (400mls (300) vs 200mls (150); $U = 32.00$; $p = 0.008$). There were 10 (13.5%) participants with ante/intrapartum EC in the intervention group and 14 (18.9%) with ante/intrapartum EC in the control group. There was a statistically significant increase in the caesarean section rate in participants in the intervention group (80.0% vs 28.6%; $\chi^2 = 6.171$; $p = 0.036$).

There was no statistically significant difference in other maternal outcomes of both groups as illustrated in Table 3.

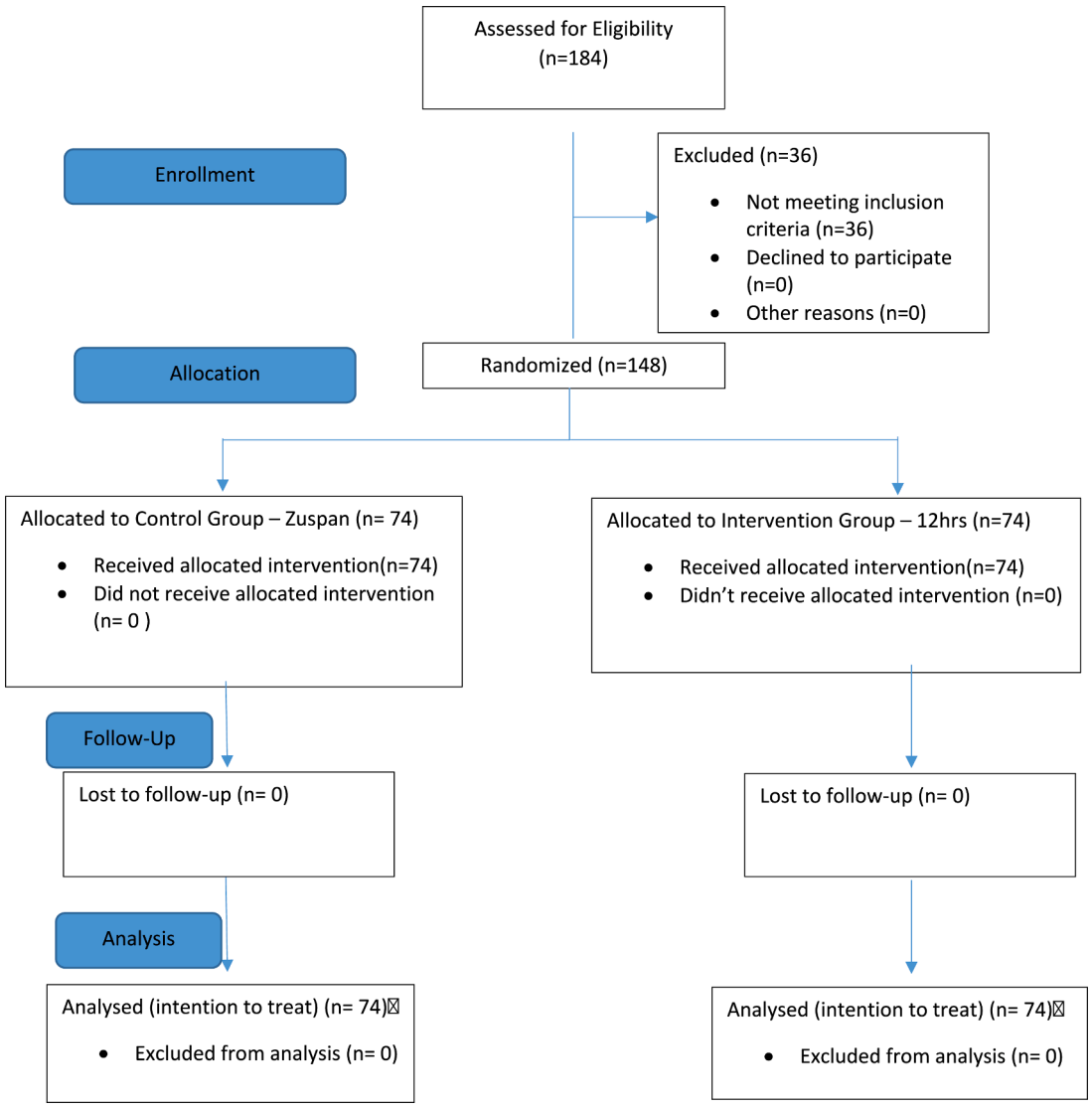

Fig. 1. CONSORT 2010 flow diagram.

There were no signs of $MgSO_4$ toxicity in both groups of parturient with EC.

The perinatal outcomes for the parturient with severe preeclampsia and eclampsia are illustrated in Table 4.

4. Discussion

This study was to compare maternal and perinatal outcomes between the intervention group – had 12 h maintenance dose of Zuspan Regimen and the control group – had 24 h maintenance dose of Zuspan Regimen in parturient with SPE and EC. It revealed no statistical difference in the occurrence and recurrence of seizures in both groups for those with both pre-eclampsia and eclampsia respectively. No participants in this study had signs of $MgSO_4$ toxicity vis a vis loss of deep tendon reflex, pulmonary oedema and respiratory depression. The blood loss at delivery was less in the intervention group in those with SPE while in those with EC, it was more in the intervention group but these differences were statistically significant. The perinatal outcomes were similar in both groups for both SPE and EC except for a significant increase in the number of days on admission in the control group of those neonates delivered to mothers with eclampsia.

Similar to the findings in the intervention arm of this study, studies by Unwaha *et al*, Abd EL Khalifa *et al.* and Anjum *et al.* [18,21,22] there was no incidence of eclampsia in the reduction of maintenance dose of $MgSO_4$. The findings in the control arm of this study (incidence of eclampsia of 1.4%) was similar to the study by Abd EL Khalifa *et al.* [21] in which the incidence of eclampsia was 1.3% (observed in the 24-hour group only), though this difference was not statistically significant.

This study revealed no incidence of PPH in the intervention group with SPE but 0.04% in the control group (both participants in the control group had abruptio placentae complicating the severe preeclampsia), similar to the study by Vigil-De Gracia *et al.* [23] in which a reduced incidence was found in the reduced maintenance group but in both studies this was not statistically significant. Though the blood loss in the intervention group with SPE was less than that of the control group, this was not statistically significant. The increase in the blood loss in the control group was affected by the blood loss in the patients with abruptio placentae. This result reveals that $MgSO_4$ though a smooth muscle relaxant may not increase the incidence of PPH when used in the management of ante/intrapartum severe preeclampsia which is also similar to the findings of the systematic review by Héman *et al.* [24] that there was no significant increase in the risk of PPH with use of $MgSO_4$. A reduction in caesarean section rate in the intervention group with SPE though not statistically significant was similar to the study by Abd EL Khalifa *et al.* [21]. The high rate of caesarean section in both groups may be attributed to unfavourability of the cervix at presentation and the fact

Table 1
Socio-Demographic characteristics of participants within treatment groups.

Characteristics	Group A (N = 74)N (%)	Group B N = 74)N (%)	P-value
Age (years)			
≤19	2 (2.7)	0 (0.0)	
20–34	58 (78.4)	55 (74.3)	
>34	14 (18.9)	19 (25.7)	0.242**
Parity			
0	35 (47.3)	34(45.9)	
1	19 (25.7)	11 (14.7)	
2	11 (14.7)	11 (14.7)	
3	3 (4.1)	6 (8.2)	
4	4 (5.4)	8 (10.8)	
>4	2 (2.7)	4 (5.4)	0.484**
Educational status			
No formal	3 (4.1)	2 (2.7)	
Formal	71 (95.9)	72 (97.3)	0.649**
Marital status			
Not currently married	2 (2.7)	4 (5.4)	
Currently married	72 (97.3)	70 (94.6)	0.405**
Occupation			
Unemployed	15 (20.3)	12 (16.2)	
Unskilled	22 (29.7)	32 (43.2)	
Semi-skilled	15 (20.3)	17 (23.0)	
Skilled	22 (29.7)	13 (17.6)	0.201
Gestational age (weeks)	(N = 66)	(N = 64)	
34–36	22 (33.3)	35 (54.6)	
37–42	44 (66.7)	29(45.4)	0.323

**Fisher's exact test.

Table 2
Clinico-biochemical parameters of participants within treatment groups.

Clinico-biochemical parameter	Group A Median (IQR)	Group B Median (IQR)	U	p-value
Age (years)	29.0 (8)	30.0 (10)	2604.00	0.607
Gestational age (weeks)	38.0 (3)	37.0 (5)	2080.00	0.458
Systolic B.P (mmHg)	170.0 (30)	170.0 (23)	2605.50	0.603
Diastolic B.P (mmHg)	110.0 (20)	110.0 (30)	2384.50	0.165
Clotting time (seconds)	200 (118)	240.0 (75)	681.50	0.073
SGOT (IU/l)	32.0 (24)	33.0 (20)	452.00	0.919
SGPT (IU/l)	24.0 (17)	24.0 (18)	447.50	0.867
Uric acid	7.0 (0.7)	6.5 (1.8)	417.00	0.413

that early and safe delivery may improve perinatal and maternal morbidity and mortality.

Similar to the study by Anjum *et al.*, El-Khayat *et al.* and Ekele *et al.* [22,25,26] (who also attempted a reduction in Pritchard regimen), there were no signs of $MgSO_4$ toxicity in the mothers with SPE. This was in contrast to the study by Unwaha *et al.* [18] in which maternal side effects like pulmonary oedema (6.3%), hyporeflexia (48.8%) were observed. This could be explained by the relatively lower concentration of the $MgSO_4$ infusion used for the maintenance regimen in this study, though the serum $MgSO_4$ levels were not measured in this study.

The non-significant increase in the recurrence of seizures in the intervention group among participants with eclampsia was in contrast to the study by Anjum *et al.* [17] who recorded recurrence of seizures only in the 24hr group (13.1%). Recurrent seizures in this study occurred within the first 12 h of maintenance dose and responded to a repeat loading dose of 2 g $MgSO_4$ but treatment failure was observed in 4 (5.26%) of the patients in the study by Anjum *et al.* [17]. The significant increase in the blood loss for eclamptics in the intervention group compared with the control group may be explained by the higher rate of caesarean section in the intervention group. The statistically significant increase in the caesarean section rate in the intervention group than the control group (80.0% vs 28.6%) might have been influenced by the less IUFD in the intervention group than control group (18.2% vs 66.7%) as caesarean section might be more apt to deliver a live baby and inappropriate for IUFD. There were no signs of $MgSO_4$ toxicity in this study as regards patients with eclampsia and this was similar to the study by Anjum *et al.* [17].

The higher perinatal mortality in the control groups with both SPE and EC was cofounded with the higher IUFD (as the IUFD occurred before enrolment into the study) in the control groups as a sub-analysis using the neonatal death revealed no significant difference. This was in contrast to findings by Unwaha *et al.* [18] which revealed a lower perinatal mortality (12.5% vs 17.5%) in the 24-hr group in participants with SPE (though not statistically significant). There was no statistical difference in the mean Apgar scores at 1 and 5 min between babies in the intervention and control groups for both severe preeclampsia and eclampsia however the mean Apgar scores at 1 and 5 min for the neonates of eclamptic mothers were lower than that of those with severe preeclampsia in both groups. This may be explained by the period of apnoea during the convulsive episodes of eclampsia resulting in respiratory and or lactic acidosis from hypoxia thus translating to a reduced oxygen supply to the foetus causing foetal hypoxia and acidosis.

There was no statistical difference in neonatal unit admission of these neonates between the intervention and control groups both severe preeclampsia and eclampsia. This was consistent with the findings in a similar study by Abd EL Khalifa *et al.* [21] on women with severe preeclampsia in terms of the loading dose regimen, 12-hour maintenance and 24 h maintenance. In neonates whose mothers had severe preeclampsia, the most common indication for NNU admission for both groups was low birth weight and this is a function of hypertensive disorders of pregnancy being a risk factor for intrauterine growth restriction and the risk of preterm delivery of these neonates [9]. Similar to the finding of Unwaha *et al.* [18], only the intervention group had neonates admitted for perinatal asphyxia though this was not statistically significant. The number of days on admission in intervention group was less than that in the control group in neonates whose mothers had SPE (though not significant) being in contrast to the study by Unwaha *et al.* [18] in which the 24-hr group had lesser mean stay on admission. This may be explained by a lower mean birth weight in the control group in this study as opposed to a lower mean birthweight in the 12 hr group in the study by Unwaha *et al.* [18]. Indications for admission were not studied in the study by Abd EL Khalifa *et al.* [21]. In neonates of mothers with eclampsia, the intervention group had 2 babies (18.2%) admitted apiece on account of low birth weight and perinatal asphyxia but all the 3 neonates admitted in NNU in the control group were admitted on account of low birth weight. No baby was admitted for respiratory distress in both groups. The number of days on admission being statistically significantly lower for those in the intervention group of neonates

Table 3
Maternal outcomes in those with SPE and EC.

	SPE				EC			
	GROUP A N = 59 n (%)	GROUP B N = 57 n (%)	χ^2	p-value	GROUP A N = 15 n (%)	GROUP B N = 17 n (%)	χ^2	p-value
Occurrence of seizures	0(0.00)	1 (0.02)	2.106	0.239**	2 (13.3)	2 (11.8)	0.018	1.000**
PPH	0(0.00)	2 (0.04)	2.277	0.221**	0(0.00)	0(0.00)	–	–
HDU Stay > 48hrs	0(0.00)	0(0.00)	–	–	1 (6.7)	2 (11.8)	0.244	1.000**

Table 4
Perinatal Outcomes of those with antepartum SPE and antepartum EC.

	SPE				EC			
	GROUP A N = 57n (%)/ median (IQR)	GROUP B N = 51n (%)/ median (IQR)	x^2/U	p-value	GROUP A N = 11n (%)/ median (IQR)	GROUP B N = 15n (%)/ median (IQR)	x^2/U	p-value
Alive	56 (98.2)	42 (82.4)			8(72.7)	3 (20.0)		
Perinatal death	1 (1.8)	9 (17.6)		**0.005**	3 (27.3)	12 (80.0)		**0.015**
IUFD	0 (0.0)	6 (11.7)			2 (18.2)	10 (66.7)		
Neonatal death	1 (1.8)	3 (5.9)	1.611	0.207	1 (9.1)	2 (13.3)		0.209
Median Apgar at 1 min	7.0 (1.0)	8.0 (1.0)	1061.5	0.120	5.0 (1.0)	4.0 (0.0)	1061.5	0.120
Median Apgar at 5 mins	9.0 (1.0)	9.0 (2.0)	1139.5	0.299	8.0 (2.0)	8.0 (0.0)	1139.5	0.299
Median birth weight (Kg)	1.90 (0.45)	1.95 (0.85)	1283.0	0.293	2.79 (0.98)	1.8 (0.0)	1283.0	0.293
Admission into NNU	20 (35.1)	19 (37.3)	0.446	0.504	4(36.4)	3(20.0)	2.357	0.236**
Indication for admission								
Low birth weight	13 (23.2)	12 (23.5)	0.014	0.905	2 (18.2)	3 (20.0)	2.100	0.429**
Respiratory distress	4 (7.0)	7 (13.7)	1.365	0.301**	–	–	–	–
Perinatal asphyxia	3 (5.3)	0 (0.0)	3.088	0.231**	2 (18.2)	0 (0.0)	2.100	0.429**
Median Number of days on Admission	9.0 (6.0)	10.0 (9.0)	129.0	0.084	3.5 (1)	10.0 (0)	0.000	**0.025**

**Fisher's exact test.

delivered to mothers with eclampsia than the control group may be explained by the lower mean birthweight in the control group (2.79 (0.98) vs 1.8 (0)).

5. Conclusion and recommendations

From this study:

- The reduction in maintenance dose of Zuspan regimen to 12 h resulted in no increase in the incidence of eclampsia in patients with severe preeclampsia or recurrence of convulsions in patients with eclampsia.
- There was no difference in the toxic/side effect profile of MgSO4 as regards the Zuspan regimen and its 12 h modification
- The perinatal outcomes in both groups were similar.

Thus, the use of 12 h modification of the maintenance dose of Zuspan regimen could be recommended for use in the management of severe pre-eclampsia and eclampsia however further studies considering the long term effects of a reduced maintenance dose of $MgSO_4$ on the neonates is required.

Ongoing from this study is a need for a IPD *meta*-analysis on the effect and efficacy of abridged regimen of $MgSO_4$ to help solve the problem of scarce resources in LMICs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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