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Original Research Article

A randomized controlled trial to assess the efficacy of 12-hour magnesium sulphate therapy compared to 24-hour regimen on maternal outcome among patients with eclampsia admitted in a tertiary care centre

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ABSTRACT

Background: Magnesium sulphate ($MgSO_4$) is the most popular anti-convulsant drug for treatment of eclampsia. Pritchard regimen is the most widely used regime worldwide where maintenance dose of $MgSO_4$ is administered for 24-hour after delivery or last fit (whichever is later). As the duration of $MgSO_4$ therapy increases, the incidence of adverse effects also increases. Therefore, the present study has been conducted to compare the maternal outcome with decreased duration of $MgSO_4$ therapy for 12-hour with that of 24 hours for patients with eclampsia.
Methods: It was an experimental study which was performed as a single centered, open labelled hospital based randomized control trial. It was conducted for 2 years (December 2019 to November 2021) among the patients of eclampsia admitted at department of obstetrics and gynaecology, AGMC and GBPH.
Results: No cases of recurrent seizures in either group with additional benefit of lesser adverse effect of toxicity of $MgSO_4$ in the 12-hour group.
Conclusions: In the present study, it has been seen that 12-hour $MgSO_4$ maintenance therapy is as efficacious as standard 24 hours therapy in controlling seizure as there was no case of recurrent seizure in either group.

Keywords: Recurrent seizure, $MgSO_4$, Maternal morbidity

INTRODUCTION

Eclampsia is an important cause of maternal morbidity and mortality worldwide, especially in the developing countries. Together eclampsia and preeclampsia accounts for approx. The 63,000 maternal deaths every year globally.[1] In India, these conditions accounts for 5% of all maternal deaths.[2]

Although eclampsia has remained a major global maternal health threat, but definitive etiology could not be established yet. So many researches are going on different aspects of eclampsia.

$MgSO_4$ is the drug of choice as anti-convulsant for treatment of eclampsia, because it is associated with significantly lower rate of recurrent seizures, lower rate of maternal deaths than that of other anti-convulsants.[3] Other advantages of $MgSO_4$ are-it is readily available, wide safety margin, affordable, anti-dote is available, easy to monitor clinically, no adverse effect on pregnancy and fetal outcome, does not affect the mode of delivery.

$MgSO_4$ acts by reducing endplate sensitivity to acetyl choline in neuro-muscular junction and reduces neuro-muscular irritability.[4] It triggers cerebral vasodilatation by blocking entry of calcium into synaptic cavity, which in turn reduces ischemia due to cerebral vasospasm, also blocks N methyl D aspartate (NMDA) receptors, thus preventing seizure genesis.[5-7]

There are various regimens of $MgSO_4$ available for the treatment of eclampsia, among them Pritchard regimen and Zuspan regimen are most popular. Pritchard regimen is the most widely used regimen worldwide. In the Pritchard regimen, the loading dose of 4 gm (20% solution) of $MgSO_4$ is given slowly over 5-10 minute, followed by 10 gm (50% solution) intramuscularly (5 gm in each buttock). Then maintained by 5 gm IM in alternate buttock 4 hourly for 24 hours after last fit or delivery whichever is later.[8]

Administration of $MgSO_4$ for 24 hours after delivery or last fit (whichever is later) is considered as best practice, but the reason behind continuing maintenance dose for 24 hours is not clearly mentioned.[9]

Studies has shown that, seizure can be effectively controlled in cases of eclampsia with short duration of $MgSO_4$ with additional benefits to both patient and health care system in terms of early recovery of mother, reduced chances of magnesium toxicity and decreased duration for intensive monitoring involving less man power, reduced cost of therapy which is particularly important in developing countries like India where infrastructure and resources are less.[10]

Although the effectiveness of $MgSO_4$ in treating and preventing eclampsia has been established, scope of research is still there regarding its dosage and duration of therapy which can further be modified.

So, it is necessary to evaluate the efficacy and acceptability of short duration (12 hours) $MgSO_4$ therapy over 24hrs therapy. The outcome of this study might help to add on the standard treatment guideline. Therefore, the present study has been conducted to compare the maternal outcome with decreased duration of $MgSO_4$ therapy for 12 hours with that of 24 hours therapy for patients with Eclampsia admitted in AGMC and GBPH.

METHODS

Study type

It was experimental study.

Study design

The study design was single centered, open label parallel group hospital based on the randomized controlled trial design.

Study place

Study conducted at Agartala government medical college and GBP hospital.

Study period

Study carried out from December 2019 to November 2021.

Inclusion and exclusion criteria

Patients admitted with eclampsia (Ante-partum, intra-partum, postpartum eclampsia) in the obstetrics and gynaecology department of AGMC and GBPH who gave consent to take part in the study were included. Patients of eclampsia with complications (acute renal failure or pulmonary edema), those with contraindication to $MgSO_4$ (e.g. drug hypersensitivity, myasthenia gravis, anuria, oliguria), or known seizure disorder, prior history of anti-convulsant intake, convulsion due to any other cause, or patient receiving $MgSO_4$ for severe preeclampsia as prophylaxis were excluded from the study.

Intervention

Informed consent from all women matching the inclusion and exclusion criteria were taken and they were included in the study. Both the group received loading dose of $MgSO_4$: 4 gm of 20% $MgSO_4$, IV slowly over 15-20 minutes followed by 5 gm of 50% solution of $MgSO_4$ intramuscularly in each buttock.

Then test group received maintenance dose of 5 gm of 50% solution of $MgSO_4$ intramuscularly in alternate buttock 4 hourly for 12 hours after delivery/ last seizure (whichever is later) and control group received same for 24 hours after delivery/last seizure (whichever is later).

All the patients were kept on indwelling catheter, fluid input and urine output chart were maintained. Every time before giving the maintenance dose respiratory rate, deep tendon reflex were checked to rule out $MgSO_4$ toxicity. Subsequent dose was given if respiratory rate was more than 16/min, Deep tendon reflex was present, urine output was more than 100 ml in the preceding 4 hours.

Rescue medication

If any patient from test group gets recurrent seizure after completion of assigned duration of $MgSO_4$ therapy during trial, she was supposed to receive $MgSO_4$ for another 12 hours from this point of time and if any patient from control group gets recurrent seizure after completion of assigned duration of $MgSO_4$ therapy during trial, she was supposed to receive $MgSO_4$ for another 24 hours from this point of time. If convulsion occurred after 30 min of initial loading dose before completion of scheduled period of $MgSO_4$ therapy, 2 gm 20% solution IV was given and previous dosage schedule

of 4 hourly injection was continued. If any patient developed toxicity of $MgSO_4$, $MgSO_4$ were withdrawn. If convulsion was not controlled by $MgSO_4$, then departmental protocol followed to control convulsion.

Objective and hypothesis

Hypothesis: 12 hours maintenance dose of $MgSO_4$ following the loading dose for management of eclampsia is not inferior than 24 hours maintenance dose of $MgSO_4$.

Primary objective: To compare the efficacy of 12 hours $MgSO_4$ therapy with that of 24 hours therapy in treatment of Eclampsia in terms of preventing recurrent seizures.

Secondary objective: To compare the outcome of 12 hours $MgSO_4$ therapy over 24 hours in treatment of Eclampsia in terms of duration of hospital stay of mother, duration of Foley's catheterization, duration of intensive monitoring, proportion of death of mother during hospital stay, proportion of $MgSO_4$ toxicity.

Outcome

Primary outcome variable: recurrence of seizure. Secondary outcome variable: duration of hospital stay of the mother, duration of catheterization, duration of intensive monitoring, maternal death, $MgSO_4$ toxicity.

Sample size calculation

Sample size for this study is calculated on the basis of % of patient experienced repeat convulsion following either 12/24 hours $MgSO_4$ regimen as primary outcome. It calculated that 51 subjects should be required per group in order to detect non-inferiority of 12 hours regimen in comparison to 24 hours regimen with non-inferiority margin of 5% with 80% power and 5% probability of type 1 error.

In this calculation it is assumed that, percentage of failure rate (recurrence of seizure) in 24-hour regimen is 1% and percentage of failure in 12-hour regimen is 2%.[10,14] Keeping a margin of 10% dropout, recruitment target is being kept 56 subject per group.

This sample size has been calculated by using the formula for non-inferiority trial

$$M=(Z_{1-\alpha}+Z_{1-\beta})^2\,[\,\pi_s(1-\pi_s)+\pi_T(1-\pi_T)]/(\pi_T-\pi_S.s)^2$$

s=non-inferiority limit of the difference in proportions
πT=proportion in test treatment
πS=proportion in standard treatment
$\pi T-\pi S$= expected difference in proportions
α=significance level
$1-\beta$=power

It is done by n Master software 2.0 (Department of biostatistics, Christian medical college, Vellore, 2011).

Randomization and sequence generation

Permuted variable block randomization was adopted. It was done by online software sealed envelope Ltd. 2017 to create a blocked randomization list online. (Available from: http://www.sealedenvelop.com/simple - randomizer/v1/lists).

Allocation concealment

It was done by sequentially numbered opaque sealed envelope.

Allocation implementation

Randomization and allocation sequence were generated by independent faculty member from department of pharmacology.

Blinding and masking

Study was open-labelled, so no blinding/masking was done.

Data collection method

Patient admitted or diagnosed with Eclampsia were recruited in the study after considering inclusion and exclusion criteria. Once they found to be eligible for recruitment, sequentially numbered sealed opaque envelope were opened and accordingly they were allocated in 12 hour or 24 hour group. All baseline data were recorded and the patients were monitored as per standard protocol for management of eclampsia.

Ethical approval

The protocol of the thesis has been approved by institutional ethical committee Agartala government medical college and GBP hospital, Agartala.

Statistical analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables.

Primary outcome variable is recurrent seizure which is categorical variable, so frequency of seizure between two groups was tested by chi-square test. Secondary outcome variables like duration of hospital stay of mother, duration of catheterization, duration of intensive care monitoring are being numerical variable, were analysed by Student t test. Secondary variables like proportion of maternal death, proportion of $MgSO_4$ toxicity between two groups were tested by chi-square test.

RESULTS

Among patients included in analysis in either group had no significant difference in terms of age, gravida, gestational age, proteinuria, BP at time of admission.

Most of the patients in either group were of less than 25 years of age followed by 26-30 years. There was no statistically significant difference in age distribution between 2 groups (Table 1).

Majority of eclampsia patients were Primi gravida. In 12 h group, 46 (82.1%) patients primi, 9 (16.1%) patients were second gravida and 1 (1.8%) patient was 3rd gravida. In 24 h group 43 (76.8%) patients were primi, 9 (16.1%) patients were 2nd gravida and 3 (5.4%) patients were 3rd gravida, 1 (1.8%) patient 4th gravida. These groups show no statistically significant difference in their distributions between gravida of patients (p=0.5517) (Table 2).

Regarding the primary outcome, no seizure recurred in either group after completion of $MgSO_4$ (Table 3).

Regarding secondary outcome, there is significantly higher total duration of hospital stay of mother, total duration of catheterization, duration of intensive monitoring and higher $MgSO_4$ toxicity in 24 h group (Table 4-7).

Table 1: Age wise distribution among patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

Age group (in years)	12 hours, N (%)	24 hours, N (%)	Statistical significance		
			Chi-square value	P value	Remarks
<25	37 (66.1)	40 (71.4)	0.5455	0.9088	Not significant
26-30	12 (21.4)	9 (16.1)			
31-35	3 (5.4)	3 (5.4)			
>35	4 (7.1)	4 (7.1)			
Grand total	56 (100)	56 (100)			

Table 2: Gravida wise distribution in patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

Gravida	12 hours, N (%)	24 hours, N (%)	Statistical significance		
			Chi-square value	P value	Remarks
Primi	46 (82.1)	43 (76.3)	2.1011	0.5517	Not significant
2nd gravida	9 (16.1)	9 (16.1)			
3rd gravida	1 (1.8)	3 (5.4)			
4th gravida	0 (0)	1 (1.8)			
Total	56 (100)	56 (100)			

Table 3: Recurrent seizure in patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy

Recurrent seizure	12 hours, N (%)	24 hours, N (%)
Yes	0 (0)	0 (0)
No	56 (100)	56 (100)

Table 4: Distribution of mean duration of hospital stay in patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

Duration of hospital stay (in days)	12 hours		24 hours		Statistical significance	
					P value	Remarks
	Mean	SD	Mean	SD	<0.0001	Significant
	3.5000	0.6030	4.5179	0.9907		

Table 5: Distribution of mean duration of foley's catheterisation in patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

Duration of Foley's catheterisation (in hours)	12 hours		24 hours		Statistical significance	
					P value	Remarks
	Mean	SD	Mean	SD	<0.0001	Significant
	25.6518	6.5809	41.4107	7.2495		

Table 6: Distribution of mean duration of intensive monitoring in patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

Duration of intensive monitoring (hours)	12 hours		24 hours		Statistical significance	
					P value	Remarks
	Mean	SD	Mean	SD		
	27.1273	6.6334	42.5357	7.4565	<0.0001	Significant

Table 7: Distribution of $MgSO_4$ toxicity among patients of eclampsia undergone treatment with either 12 hours or 24 hours of $MgSO_4$ maintenance therapy.

$MgSO_4$ toxicity	12 hours, N (%)	24 hours, N (%)	Statistical significance		
			Chi-square value	P value	Remarks
Toxicity present	4 (7.1)	12 (21.4)	4.6667	0.0307	Significant
No toxicity	52 (92.9)	44 (78.6)			
Total	56 (100)	56 (100)			

DISCUSSION

As per our study, there were no cases of recurrent seizures in either group. This is a significant finding for improving patient management in low resource nations.

Nautiyal et al showed that they aimed to compare the efficacy of low dose regimen of $MgSO_4$ with Pritchard's regimen in patients of eclampsia.[11] A prospective cross-sectional study was carried out. Low dose regimen was equally effective in controlling the seizures and only two patients (6.6%) had recurrent seizures, (p=1.00).

We showed that in 12 hours group, 4 (7.1%) patients had $MgSO_4$ toxicity. In 24 hours group, 12 (21.4%) patients had $MgSO_4$ toxicity.

Distribution $MgSO_4$ toxicity between two groups was statistically significant.

Ranganna et al determined there was one case of seizure in each group (2%).[2] There were 6 cases of absent knee jerk and 4 cases of oliguria in those receiving the 24-hour $MgSO_4$ while none of these complications were seen in those receiving only the loading dose (p=0.012, p=0.022). Conclusion: The loading dose of the modified Pritchard's regime alone may be effective in preventing seizures in patients of severe pre-eclampsia with the added advantage of reduced toxicity and better neonatal outcome.

In the present study, in 12 hours group, the mean duration of Foley's catheterization (mean±SD) of patients was 25.6518±6.5809.

In 24 hours, group, the mean duration of Foley's catheterization (mean±SD) of patients was 41.4107±7.2495.

There is statistically significant difference in the mean duration of Foley's catheterization between the two groups.

In 12 hours, group, the mean duration of intensive monitoring (mean±SD) of patients was 27.1273±6.6334.

In 24 hours, group, the mean duration of intensive monitoring (mean±SD) of patients was 42.5357±7.4565.

There is statistically significant difference in the mean duration of intensive monitoring between the two groups.

Anjum et al studied maternal outcome after 12 hours and 24 hours of $MgSO_4$ therapy for eclampsia, it was seen that, the mean duration of monitoring was 19.3±4.9 hours in the 12 hours group as compared with 31.8±4.7 hours in the 24 hours group.[12] The mean duration of Foley's catheterization was 19.6 hours in 12 hours group and 31.5 hours in 24 hours group.

In the present study, no maternal mortality was reported, a finding that is similar to the results of Vigil-De-Gracia et al in a randomized multicenter open study which compared the benefits of $MgSO_4$ for 24 hours postpartum vs 6 hours postpartum in patients who received the drug for less than 8 hours before delivery.[13]

Limitations

It was a single centered study with a smaller number of cases, study findings need validation from adequately powered, well designed, large scale RCTs with bigger sample size with multiple health facility.

CONCLUSION

In the present study, it is seen that 12 hours $MgSO_4$ maintenance therapy is as efficacious as standard 24 hours therapy in controlling seizure with additional benefit of lesser adverse effects, early ambulation of mother, lesser duration of indwelling catheter, and intensive monitoring, also lesser hospital stays which were beneficial to both patient and health care system. With efficacy comparable to Pritchard regimen and lesser

adverse effects, in coming years, shorter duration of $MgSO_4$ therapy may become an established treatment protocol and will be a major stepping stone towards the aim of safe motherhood.

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