ORIGINAL RESEARCH PAPER

Gynaecology

POSTPARTUM PROPHYLAXIS WITH SHORTCOURSE MAGNESIUM SULPHATE REGIME IN WOMEN WITH SEVERE PREECLAMPSIA

KEY WORDS: Magnesium Sulphate, Severe Preeclampsia , Shortcourse

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ABSTRACT

OBJECTIVE: To compare the effectiveness of 12 hours short course postpartum magnesium sulphate therapy versus 24 hours standard regime in stable patients with severe preeclampsia.

METHODS: This randomized controlled trial on 100 women with severe preeclampsia was conducted in a tertiary hospital, between 2017-2018. Fifty women received postpartum MgSO4 for 12 hours and 50 for 24 hours. Groups were compared for occurrence of eclamptic fit, side effects , toxicity profile, & feto maternal outcome.

RESULTS: The two groups did not have any significant difference in gestational age, gravidity, BMI, blood pressure, proteinuria, antihypertensive use , side effects, ICU admission, and toxicity profile. Two women from either group developed convulsions and MgSO4 was reinstituted for 24hours. Diuresis in 12 hour group was statistically significant. Increased NICU admission and perinatal deaths in both groups were due to prematurity.

CONCLUSION: Short course postpartum MgSO4 therapy in stable women with severe preeclampsia was equally effective as the 24 hours therapy with similar feto-maternal outcomes and added benefits of reduced total drug dose and side effects.

INTRODUCTION

Pre-eclampsia is a pregnancy-specific multisystem disorder , usually characterized by hypertension and proteinuria after 20 weeks of gestation.[1] Hypertensive disorder complicates 5-8% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality. Pre-eclampsia and eclampsia contribute to 12% of all maternal deaths in developing countries. Morbidity and mortality with preeclampsia are totally preventable with adequate and early interventions.[2]

Severe preeclampsia may progress to eclampsia with occurence of seizures, which could be significantly reduced by administration of Magnesium Sulphate ($MgSO_4$)[3]. The landmark MAGPIE TRIAL in 2002 concluded that prophylactic MgSO4 can reduce the risk of eclampsia by 50%.[4]

Traditionally, seizure prophylaxis has been administered intrapartum and continued postpartum for an arbitrary time, usually 12-24 hours, as eclamptic seizures occur during the postpartum period with the greatest risk being in the first 12 – 24 hours after delivery. [5]

The rationale behind administration of prophylactic magnesium sulphate in women with severe preeclampsia is that, for every 10 preeclamptic women treated with magnesium sulphate, seizures could be prevented in one, thereby reducing the consequent maternal morbidity.

The ACOG (2001) and RCOG (2006) guidelines recommend the initiation of seizure prophylaxis for severe preeclampsia in labour and its continuation after delivery. There are no existing guidelines on the duration of postpartum seizure prophylaxis. Many trials have been conducted to compare the standard regimen of MgSO4 with the abbreviated regimen[6,7,8].Reducing the duration of postpartum MgSO4 administration will reduce the need for intensive monitoring of vitals and urine output.

Most patients with preeclampsia respond promptly to delivery with a lowering of blood pressure, diuresis and general clinical improvement. Such women are considered to be at a lower risk of developing eclampsia. An abbreviated postpartum therapy for 12 hours was suggested for these women at low risk for seizures. A standard regime for the treatment of preeclampsia for a predetermined time in the postnatal period may not be required in such women.

Many trials have suggested an individually determined postpartum magnesium sulphate protocol based on patient clinical parameters in women with preeclampsia[9].

In our institution, postpartum seizure prophylaxis with magnesium sulphate for severe preeclampsia is continued for twenty-four hours after delivery in all women who had received the drug during intrapartum period.

Hence, this study was conducted to compare the effectiveness of 12 hours short course postpartum magnesium sulphate therapy versus 24 hours standard magnesium sulphate postpartum prophylactic maintenance therapy in stable patients with severe preeclampsia, in preventing convulsions and to study the side effects with both regimes.

MATERIAL AND METHODS:

This randomized controlled trial was conducted at the Thanjavur medical college and hospital ,Tamilnadu, India, between April 2017 and April 2018. This study was approved by the Research and ethics committee of Thanjavur Medical College, Thanjavur. There were 11,200 deliveries during the study period. Out of these, 100 women with severe preeclampsia were enrolled in the study after obtaining informed consent.

A. INCLUSION CRITERIA:

All women with severe preeclampsia i.e. women with new onset proteinuric hypertension along with atleast one of the following criteria were included in this study

- SBP ≥ 160 mmHg or DBP ≥ 110 mmHg.
- Proteinuria ≥ 2+ by dipstick.
- Serum creatinine >1.2 mg/dl.
- Platelet count < 1 lakh/cubic.mm
- AST elevated two times above upper normal limit.
- Persistent headache / blurring of vision / epigastric pain.

B. EXCLUSION CRITERIA

- Refusal of participation
- Eclampsia
- Associated maternal disease like epilepsy, chronic hypertension
- Contraindications to $MgSO_4$ - hypersensitivity, oliguria < 25 ml/hour, anuria, myasthenia gravis.
- Written informed consent was obtained from the patient or relatives after explaining the procedure and the drug effects.

METHODOLOGY:

Patients were randomly assigned by using computer generated random table to 12 hours group and 24 hours group.12 hours group was designated as study group receiving $MgSO_4$ 12 hours postpartum maintenance therapy after receiving the full loading dose of $MgSO_4$. 24 hours group was designated as control group

receiving standard Pritchard regimen.

Pritchard's intermittent intramuscular regimen was followed in the control group. The loading dose was four grams of 20% magnesium sulphate solution given intravenously over 15-20 min followed by 5 grams of 50% MgSO4 solution along with 1 ml lignocaine given as deep IM in both buttock. The maintenance dose was 5 grams of 50% MgSO4 solution, IM every 4th hourly in alternate buttock, until 24 hours after delivery or last episode of fit, whichever is later provided, patellar reflex is present, respiratory rate is >16/min, urine output is atleast 100 ml in preceding 4 hours.

Both groups were monitored & managed individually for delivery & same antihypertensives were used. Variables such as maternal morbidities, side effects of MgSO4 during therapy and 6 hours after the last dose , need for IV antihypertensive therapy, urine output during MgSO4 therapy and mode of delivery were compared between the two groups.

A detailed history was obtained from the patients. General examination and obstetric examination were done. Baseline parameters like height, weight, pulse rate, blood pressure, respiratory rate, gestational age, fetal heart rate, Bishop's score and adequacy of pelvis were recorded. Routine investigations such as hemoglobin, haematocrit, CBC, .liver function tests, renal function tests coagulation profile and urine albumin were done. Urine output was monitored.

ANALYSIS:

Data were entered in the excel spread sheet and variables were coded accordingly. The statistical analyses were performed using Graph pad Prism version 5 software. Data were presented as frequency with proportion n(%) for categorical variables. Unpaired 't' test was used to compare the means between the groups which follows parametric distribution. Fisher's exact test (for sample <30) was used to compare the proportions between the groups as appropriate. $p<0.05$ was considered statistically significant.

Primary outcome studied in our trial was the comparison of efficacy of short course postpartum magnesium sulphate therapy in women with severe preeclampsia (12hours) with the standard regime (24 hours). The secondary outcome studied was the occurence of side effects and toxicity profile in both the groups.

RESULTS:

The interventional group and control group, generated by randomization were well balanced with 50 women in each group. Baseline characteristics in both groups were well matched.

Table. 1: Baseline demographic & clinical characteristics:

S.No	Characteristics	12hrs group (n = 50)	24hrs group (n = 50)
1	Age (years)	23.6 ± 3.4	26.3±3.5
2	Gestational age (weeks)	35.8±3.6	35.6±2.7
3	BMI	23.4±1.4	27.1±2.2
4	Parity: Primigravida Multigravida	25(50%) 25(50%)	17(34%) 33(66%)
5	Systolic BP (mmHg)	155.2 ± 11.8	154.2 ± 11.7
6	Diastolic BP (mmHg)	106.2 ± 7.25	104.4 ± 8.1
7	Proteinuria: 2+ 3+ 4+	 22(44%) 25(50%) 3(6%)	 14(28%) 26(52%) 10(20%)
8	Mode of delivery: Vaginal delivery Caesarean section	 36(72%) 14(28%)	 38(76%) 12(24%)
9	Prematurity	23(46%)	29(58%)
10	Urine Output: 0-12hrs (ml) 12-24hrs (ml)	 579 ± 110 657 ± 103	 572±13.7 509 ± 107

There were no statistically significant differences in the age, parity and gestational age among both groups. The BMI, proteinuria, systolic and diastolic blood pressure and mode of delivery were also not significantly different in both the groups.

Headache and vomiting were the common imminent symptoms in both the groups. Nearly one third of women with severe preeclampsia were on oral antihypertensive drug before initiating prophylactic $MgSO_4$ therapy, which was 32% in the study group and 38% in the control group.

Table. 2: Maternal outcome:

S.NO	Characteristics	12hrs group (n = 50)	24hrs group (n = 50)	P value
1	Occurrence of fit	2(4%)	2(4%)	>0.9
2	Maternal ICU admission	6(12%)	8(16%)	0.47
3	Maternal toxicity: Absent tendon reflex Oliguria	2(4%) 2(4%)	3(6%) 4(8%)	0.213
4	Side effects: Burning Sensation Flushing Thirst Vomiting	 21(42%) 15(30%) 10(20%) 7(14%)	 28(56%) 8(16%) 7(14%) 12(24%)	
5	6 hours after cessation of $MgSO_4$ Pain at injection site Drowsiness Lethargy	 24(48%) 18(36%) 11 (22%)	 36(72%) 33(66%) 27(54%)	 0.002 0.004 0.0018
6	Hospital stay (days)	9.82.6	9.92.5	0.7
7	Need of antihypertensive drug at discharge	50(100%)	50(100%)	

2/50 women (4%)in the study group developed convulsions- one 48 hours after cessation of MgSO4 therapy and another 72 hours later. On MRI evaluation, both were diagnosed with posterior reversible encephalopathy syndrome. Similarly, 2/50 (4%) of women in the control group also developed convulsion on 5th and 7th postnatal day and on evaluation, MRI Brain was normal in both.

HELLP syndrome was the most common reason in the intervention group for continual care in Intensive Care Unit. AKI and HELLP syndrome among the control group were the reasons for ICU care. None developed PPH among both the group.

50% of the intervention group and 44% of the control group had no side effects during $MgSO_4$ therapy. and Six hours after cessation of MgSO4 therapy,minor side effects were observed more in the control group compared to the study and was statistically significant Fetal distress was the indication for LSCS in 21% of the interventional and 25% in the control group. As $MgSO_4$ also has tocolytic effects, failed induction for cesarean section, hospital stay and need of antihypertensive drug at discharge was compared and found to be almost the same in both groups.

On studying the neonatal outcome there was no statistically significant difference between both the groups regarding birth weight, prematurity, NICU admission and perinatal mortality.

Table.3: Neonatal outcome:

S.NO	Characteristics	12hrs group (n = 50)	24hrs group (n = 50)	P value
1	Birth weight Prematurity NICU admission Perinatal mortality	2.3±0.6 23(46%) 16(32%) 4(8%)	2.4±0.5 29(58%) 16(32%) 5(10%)	0.582 0.2 >0.9 0.222

DISCUSSION:

$MgSO_4$ is the anticonvulsant of choice in severe pre eclampsia to prevent the onset of eclampsia and reduce the frequency of seizure in eclamptic patients. It is still used with reluctance in some places because of the fear of toxicity i.e respiratory depression. Many trials have been conducted with varying protocols of $MgSO_4$ regime and with varying duration of therapy. Our study was aimed to study the feasibility of reducing the duration of postpartum

$MgSO_4$ therapy in stable women with severe preeclampsia.

In studies similar to ours , Shaheen et al, Sabina et al, Maryam et al had compared the 12 hours postpartum $MgSO_4$ therapy with the standard 24 hours regime and found that the abbreviated 12 hour therapy was as effective as the 24 hour therapy[10,11,12,] . While Shaheen et al and Sabina et al had observed no eclamptic fit in the 12 hour group ,Maryam et al reported a single case of eclamptic fit requiring extended $MgSO_4$ therapy[10,12]. Similar observations were made by few other authors also[13,14] In our study, 2 women in either groups developed seizures. While the two women in study group developed seizures 48 hours and 72 hours after cessation of $MgSO_4$ therapy, the 2 in the control group developed seizures on the 5 th and 7th postnatal day. $MgSO_4$ therapy was reinstituted in all 4 women. On evaluation, the two women in study group who developed convulsions were diagnosed with posterior reversible encephalopathy syndrome, while MRI Brain was normal in the 2 women in the control group.

Isler et al used individual patient clinical parameters to signal cessation of postpartum $MgSO_4$ seizure prophylaxis in pregnancy related hypertensive disorders and reported that clinical criteria rather than arbitrary protocols can be used successfully to shorten the duration of postpartum $MgSO_4$ therapy for seizure prophylaxis[15] .

Fontenot et al used inadequate postpartum diuresis as a criteria for the cessation of $MgSO_4$ therapy in severe preeclampsia and compared the outcome with the control group[16]. Ascarelli et al observed significant diuresis in the 12 hours group without need for reinstitution of $MgSO_4$ therapy[9]. In our study significantly better diuresis was observed in the 12hours $MgSO_4$ group compared to that of 24 hours $MgSO_4$ group.

MAGPIE trial showed that only 25% of women developed side effects of $MgSO_4$ compared to 5% in placebo arm [4]. We observed no statistically significant difference with regard to major side effects in either groups. The common side effects observed in our study were generalized burning sensation and flushing which were similar to that reported by Maryam et al and MAGPIE trial[4,12]. In our study, women in the 24 hours group reported a higher incidence of minor side effects like pain at the injection site ,drowsiness and lethargy 6 hours after cessation of therapy when compared to the 12 hours group and it was statistically significant.

In their randomized trial comparing loading dose with conventional 24 hours prophylactic MgSO4 therapy, Ranganna et al observed a higher incidence of $MgSO_4$ dose deferral in 24 hours group ,though it was not statistically significant.[17] In our study $MgSo_4$ was withheld in 8% in 12hours group and 14% in 24 hours $MgSO_4$ therapy group. The most common cause for dose deferral was absent deep tendon reflexes in both the groups.

None of the women in our study developed respiratory depression since criteria for withholding MgSO4 was strictly followed.. A similar observation has been reported by several authors[12,13,14]. Maternal ICU admission in our study was 12% in the intervention group similar to that observed by W.Elkhayat et al and were due to complications like HELLP, DIVC ,AKI and eclampsia. [18] There was increased NICU admission in both the groups of our study which was due to prematurity.

The drawback of our study is the sample size which might have been insufficient to detect the differences between the two groups in terms of side effects , toxicity of MgSO4 and occurrence of fits. From this study, we found that the short course postpartum magnesium sulphate therapy in severe preeclampsia was found to be as effective as 24 hours seizure prophylaxis. MgSO4 toxicity profile and its efficacy in preventing eclamptic fits were similar in both groups. Till now the debate about the ideal duration of postpartum $MgSO_4$ as an anticonvulsant is continuing[19].

Although the earlier works by Ascarelli et al , M.Kashanian et al ,Ehrenburg et al, Isler et al, and were different from this study in design and methodology, the objective of all was to ascertain the feasibility of short course postpartum seizure prophylaxis in severe preeclampsia without the risk of eclampsia[9,12,13,15]

$MgSO_4$ could then be safely administered for lesser time in selective women with severe preeclampsia found to be at low risk of postpartum eclampsia who will have satisfactory diuresis during $MgSO_4$ therapy.

CONCLUSION

Short course 12 hours postpartum $MgSO_4$ regime seems to be an effective alternative in women with severe preeclampsia who are at low risk for eclampsia with added benefits of reduced total drug use, lesser side effects and better diuresis. However , more trials with larger sample size need to be conducted to arrive at a robust conclusion regarding the safety and efficacy of short course MgSO4 therapy.

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