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Research Article

Randomized comparative study between short duration (4 hour) vs. 24 hour post-partum magnesium sulphate therapy in severe preeclampsia

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ABSTRACT

Background: Objective: To assess the safety and efficacy of shorter duration of magnesium sulphate therapy given till 4 hours after delivery as compared to the standard duration of 24 hours postpartum therapy, given to prevent eclampsia in patients with severe preeclampsia.
Methods: A prospective randomized controlled study of magnesium sulphate therapy in women with severe preeclampsia was conducted with 50 patients each in control and study group. The control group received 24 hours of postpartum magnesium sulphate therapy and the study group received for 4 hours or one intramuscular dose in postpartum period. Chi square and unpaired "t" test were used for statistical analysis of data; a probability value of <0.05 was considered statistically significant.
Results: There was no statistically significant difference in demographic data, disease severity, maternal and perinatal outcome. The need for IV anti-hypertensive postpartum was significantly higher in study group (12% vs. 0%, P=0.03). No patient developed eclampsia or required reinitiation of therapy. At the end of therapy serum magnesium levels were significantly lower in the study group.
Conclusions: In patients with severe preeclampsia shorter duration (4 hours or one dose) of postpartum magnesium sulphate therapy, is as effective as the standard 24 hours of postpartum therapy.

Keywords: Preeclampsia, Postpartum, Magnesium sulphate, Short duration therapy

INTRODUCTION

Preeclampsia is the most common medical complication of pregnancy. Hypertensive disorder complicates 5%-10% of all pregnancies. Preeclampsia complicates 2% to 8% of all pregnancies. Severe preeclampsia is associated with increased risk of maternal morbidity and mortality; of which progression to eclampsia is the major cause.[1,2] In developing country a woman is seven times as likely to develop preeclampsia than a woman in a developed country.[3] Eclampsia complicates 1-2% of severe preeclampsia. In developing countries development of eclampsia in case of preeclampsia is 10-30 times more common than developed countries.[4] Preeclampsia and eclampsia accounts for 24% of maternal deaths in India.[5] Maternal death is largely from complications like abruptio placentae, hepatic failure and eclampsia.[6]

Preeclampsia patients those who are not receiving seizure prophylaxis 3.9% of them develop eclampsia while only less than 1% of them develop eclampsia who are receiving such therapy.[7] Routine use of magnesium sulphate in the prevention of eclampsia among patients with severe preeclampsia is an accepted standard of care.

Usually it is initiated before delivery and continued for varying periods after delivery commonly until 24 hours.[7]

Today, magnesium sulphate is administered commonly as a continuous intravenous infusion or Pritchard's intermittent intramuscular (IM) regimen.[2] After a 4 gm intravenous loading dose the serum magnesium levels observed with intermittent intramuscular regimen and those observed with the maintenance intravenous infusion of 2 g per hour are similar.[2]

The choice of which regimen to use depends on availability of resource setting, staff to monitor as well as the expertise of the staff. While the IM regimen has the disadvantage of painful injections, it has the advantage of greater convenience and safety.[8] In our low resource setting, pumps for IV infusion are not readily available and the nursing staffs may be too busy to provide the continuous monitoring, the intramuscular route is safer. So we have used Pritchard's intramuscular regimen which is regularly used in our institution for this study.

Use of magnesium sulphate therapy is not without complications, consequently longer duration therapy possesses the risk of magnesium toxicity such as respiratory depression, renal and neuromuscular dysfunction. Risks of these complications require regular supervision; hence it is particularly important to assess the minimum effective duration of treatment. Fontenot et al. (2005), proposed that shorter duration of magnesium sulphate therapy in postpartum period (4-8 hour) must be sufficient with maternal surveillance for prevention of eclampsia in severe preeclampsia, thus avoiding the potential dangerous side effects of the longer therapy.[7] In our low resource setting with high number of deliveries, postpartum short duration of magnesium sulphate will be easier for monitoring and patient care also in addition to less side effects for mother. So we have decided to give postpartum magnesium sulphate only upto 4 hours or one intramuscular dose in the study group which will be effective till 4 to 8 hours. The approach is to give only a standard minimum cumulative dose of magnesium sulphate with continued maternal monitoring till 24 hours postpartum and reinitiate in cases only when indicated.

The present study is a randomized controlled study to investigate the efficacy and safety of shorter duration of postpartum magnesium sulphate therapy in preventing development of convulsions in cases of severe preeclampsia.

METHODS

This study is a prospective randomized controlled trial that was approved by institutional ethics committee, conducted at department of Obstetrics and Gynecology, Maulana Azad Medical College and associated Lok Nayak Hospital New Delhi and involved human subjects with severe preeclampsia. The study was conducted over a period of 17 months.

Potential subjects who fulfilled diagnostic criteria for severe preeclampsia were invited to participate in this trial. Severe preeclampsia is diagnosed with presence of one or more clinical features of-sustained systolic blood pressure of ≥160 mmHg; sustained diastolic blood pressure of ≥110 mmHg; proteinuria ≥2+ on dipstick or ≥5g/24 hour urine collection; oliguria(urine output <500 ml in 24 hours or <30 ml/hour unresponsive to a 500 ml intravenous fluid challenge); presence of persistent headache, visual disturbances, or epigastric or right upper quadrant pain; thrombocytopenia; impaired liver function; pulmonary edema or cyanosis; fetal growth restriction; or superimposed preeclampsia with preexisting chronic hypertension (hypertension before 20 weeks gestational age that was accompanied by new onset proteinuria or sudden increase in proteinuria, a sudden increase in blood pressure that met severe criteria and did not respond to medical therapy, or the presence of other severe preeclampsia criteria). Patients with eclampsia, who were on antiepileptic drugs, patients of severe preeclampsia with renal failure or respiratory failure and severe preeclampsia planned for continuation of pregnancy were excluded from the study.

As per a previous study the need for the reinitiation of therapy or the failure rate among patients who had received magnesium sulphate therapy for at least 24 hours postpartum appeared to be <0.6%.[7] Taking a confidence interval of 95%, power of 80%, and ratio of control to study subjects as 1:1, and the assumption of a need to reinitiate therapy rate of 0.5% in the control group, in the study group for detection of therapy failure rate or a need to reinitiate therapy rate 20% sample size with 46 patients in each group was calculated. Written informed consent was taken from subjects after explaining the study. A computer generated table of random numbers was used to assign patients to 1 of 2 treatment groups with a 1:1 ratio of control to study subjects.

Therapy with magnesium sulphate was initiated before delivery with simultaneous induction of labor with prostaglandin gel, oxytocin or a combination of both depending on the requirement. Control group received intra-muscular magnesium sulphate according to Pritchard's regimen, i.e. loading dose of 4 gm intravenous and 5 gm intramuscular in each buttock followed by maintenance dose of 5 gm intramuscularly every 4 hours till 24 hours postpartum. Study group received magnesium sulphate according to Pritchard's regimen, every 4 hours till 4 hour or one dose post-partum.

Hypertension was controlled by giving antihypertensive drugs according to hospital protocol. In case of acute severe hypertension i.e. blood pressure systolic ≥160 mmHg and/or diastolic ≥110 mmHg, intravenous labetalol was given. Oral antihypertensive drugs were added to the treatment if blood pressure still remains ≥150 mm of Hg systolic and/or ≥100 mm of Hg diastolic.

Oral antihypertensive drugs used in divided doses were tablet labetalol (a maximum of 2400 mg/day), tablet α methyl dopa (a maximum of 2000 mg/day), tablet nifedipine (a maximum of 30 mg/day) or combination of the two/three drugs. All patients had a Foley's catheter in place till magnesium sulphate is given and were monitored hourly for the vital signs, urine output, and deep tendon reflexes in the labor room for at least 24 hours after delivery. Indications to continue or reinitiate therapy included persistent or recurring central nervous system symptoms, eclampsia, or worsening disease severity, which was defined as increasing transaminase levels or worsening thrombocytopenia after the discontinuation of therapy. If the condition was stable and the patient no longer received magnesium sulphate therapy 24 hours after delivery, the patient was transferred to a postpartum unit where vital signs and urine output were monitored every 4 to 6 hours. Patients did not receive antihypertensive therapy unless they had persistent systolic blood pressure of >150 mmHg or diastolic blood pressure of >100 mmHg. The maintenance dose of magnesium sulphate was deferred in case the signs of drug toxicity appear i.e. if respiratory rate <12/min or urine output <30 ml/hour or absent tendon reflexes. In the study group if the patients develop symptoms and signs of imminent eclampsia, severe hypertension not responding to medication at or any time after 4 hours postpartum then the magnesium sulphate therapy would be continued till 24 hours as in the control group. And that would have considered as the failure of the therapy under study. Before start of therapy and just before the last dose of magnesium sulphate 3 ml blood sample was taken for serum magnesium level estimation. Serum magnesium levels were estimated by dye binding colorimetric method in the department of Biochemistry, Maulana Azad Medical College.

In both the groups, occurrence of eclampsia, need for reinitiation of therapy was noted. In each case mode of delivery, any maternal morbidity or mortality, number of deferred doses and the reason each time and neonatal outcome was noted. For statistical analysis, the chi square test was used to determine statistical significance for categorical variables whereas unpaired t test was used for comparison of continuous variables. A P value <0.05 was taken as level of statistical significance. Data was analysed using the SPSS (statistical software) PC version 17.0.

RESULTS

There were 120 eligible severe preeclampsia cases during the study period and 20 were excluded from the study who did not met inclusion criteria. Hundred subjects who met the inclusion criteria were enrolled. Fifty patients each were randomized to control and the study group. Demographic data and criteria for severe disease are presented in Table 1. There were no differences between groups. Maternal treatment and labor and delivery data are presented in Table 2. Between groups, there were no significant differences in antepartum mean blood pressure level or laboratory results or the duration of magnesium sulphate therapy before delivery. There were no differences in mean postpartum blood pressures, laboratory results. The need for IV anti-hypertensive postpartum was higher in study group (6 cases vs. 0 case) and it was statistically significant (P=0.03). No patient had eclampsia, required the reinitiation of therapy, or was readmitted after discharge. There were no differences in the outcome measures. Table 3 shows the adverse effects of magnesium sulphate therapy in both the groups and Table 4 gives neonatal outcome data. There were no differences between groups that related to adverse effects, birth weight, length of stay, or neonatal complications.

Table 1: Demographic data and criteria of severity.

Characteristics	Study group (N=50)	Control group (N=50)	P value
Age(years)[a]	25.66 ± 3.18	26.02 ± 2.68	0.54
Primigravida N (%)	26 (52%)	17 (34%)	0.07
Diagnosis at gestational age (weeks) [a]	36.34 ± 1.93	36.06 ± 1.97	0.47
Delivery at gestational age (weeks) [a]	36.34 ± 1.93	36.06 ± 1.97	0.47
Previous hypertension [a]	05 (10%)	05 (10%)	1.00
Severe disease criteria:			
Severe hypertension N (%)	15 (30%)	17 (34%)	0.67
CNS symp. N (%)[b]	15 (30%)	17 (34%)	0.67
ALT raised N (%)[c]	01 (2%)	03 (6%)	0.62
Epigastric pain N (%)	07 (14%)	12 (24%)	0.31
Severe proteinuria N (%)	36 (72%)	34 (68%)	0.46
IUGR N (%)[d]	11 (22%)	14 (28%)	0.64
Thrombocytopenia N (%)	0 (0%)	1 (2%)	1.00
Fundus retinopathy N (%)	01 (2%)	03 (6%)	0.62

[a]Data presented as mean ± SD, [b]CNS symp-headache, blurring of vision etc., [c]ALT - Alanine aminotransferase, [d]IUGR - Intra uterine growth restriction. Other data are number & percentages

Table 2: Maternal treatment, and delivery data.

Maternal parameter	Study group (N=50)	Control group (N=50)	P value
Caesarean delivery N (%)	13 (26%)	12(24%)	**0.95**
Antepartum SBP (mm/Hg)[a]	170.76 ± 11.99	168.60 ± 11.53	**0.36**
Antepartum DBP (mm/Hg)[a]	115.20 ± 5.84	114.68 ± 5.29	**0.64**
I/V anti-hypertensive N (%)	46 (92%)	43 (86%)	**0.34**
Antepartum oral antihypertensive N (%) 1 drug 2 drug 3 drug	 30 (60%) 15 (30%) 02 (4%)	 30 (60%) 14 (28%) 03 (6%)	**0.97**
Antepartum creatinine [a]	0.78 ± 0.23	0.79 ± 0.25	**0.86**
Antepartum hematocrit [a]	32.12 ± 2.78	33.42 ± 3.83	**0.06**
Antepartum serum uric acid	5.36 ± 0.63	5.42 ± 0.66	0.64
Serum magnesium level at 0 hour [a]	1.92 ± 0.49	1.95 ± 0.39	**0.74**
Serum magnesium at end of study [a]	5.24 ± 0.79	6.11 ± 1.02	**0.0001***
Antepartum mag. sulph. duration (hour)[a]	15.36 ± 5.38	15.1 ± 5.21	**0.81**
Postpartum SBP [a]	134.56 ± 3.94	134.52 ± 3.54	**0.96**
Postpartum DBP [a]	91.66 ± 1.86	92 ± 1.88	**0.36**
Postpartum oliguria N (%)	0 (0%)	02 (4%)	**0.49**
Postpartum hematocrit [a] (%)	29 ± 0.04	28 ± 0.02	0.12
Post-partum serum creatinine [a](mg)	0.76 ± 0.21	0.75 ± 0.22	0.82
Post-partum serum uric acid [a](mg)	5.41 ± 0.63	5.45 ± 0.62	0.75
Postpartum IV antihypertensive therapy N (%)	06 (12%)	0 (0%)	**0.03***
Post-partum hospital stay (no of days) [a]	4.24 ± 0.71	4.16 ± 0.77	0.59
Anti-hypertensive at discharge N (%)	14 (28%)	13 (26%)	0.60

[a]Data presented as mean ± SD, SBP - Systolic blood pressure in mmHg, DBP - Diastolic blood pressure in mmHg

Table 3: Side effects of magnesium sulphate therapy.

Therapy & symptoms	Study group (N=50)	Control group (N=50)	P value
Loss of DTR N (%)[a]	07 (14%)	12 (24%)	0.31
Oliguria N (%)	03 (6%)	07 (14%)	0.32
Deferred doses N (%) 0 1 2 3	 08 (16%) 42 (84%) 06 (12%) 02 (4%) 0 (0%)	 16 (32%) 34 (68%) 10 (20%) 04 (8%) 02 (4%)	 0.10 0.21

[a]DTR - Deep tendon reflexes

Table 2 shows Serum magnesium levels. At start of therapy the mean value of magnesium in the control group and the test group were not statistically significant (1.95 ± 0.39 vs. 1.92 ± 0.49 mg/dL; P=0.74). However at the end of the study the two groups had significantly different magnesium levels (6.11±1.02 vs. 5.24 ± 0.79 mg/dL; P=0.0001). This suggests that a higher concentration of magnesium sulphate remain in the plasma when it is given for a longer duration.

Table 4: Neonatal outcome.

Neonatal outcome	Study group (N=50)	Control group (N=50)	P value
Birth weight (gm)[a]	2455.1 ± 384.1	2391.8 ± 378.4	0.49
Apgar at 1 minute[a]	8.4 ± 1.85	8.1 ± 2.2	0.46
Apgar at 5 minute[a]	8.62 ± 1.78	8.44 ± 2.2	0.65
NICU admission required N (%)	08 (16%)	10 (20%)	0.79
Neonatal respiratory depression N (%)	03 (6%)	05 (10%)	0.71
SGA N (%)	07 (14%)	10 (20%)	0.59
MSB N (%)	02 (4%)	03 (6%)	1.00

[a]Data presented as means

In the present study in 10 patients (20%) in the study group and in 19 patients (38%) in the control group maintenance dose of magnesium sulphate was omitted due to clinically apparent loss of deep tendon reflexes and/or oliguria. Loss of deep tendon reflexes was the

most frequent reason for omitting the dose. In the study group the mean value of serum magnesium at which signs of toxicity appeared was 6.7 ± 0.62 mg/dl. In the control group this value was 7.14 ± 1.04 mg/dl (P=0.41). But the mean serum magnesium value at end of study who developed toxicity symptom was 6.38 ± 1.15 vs. those who did not had symptoms was 5.45 ± 0.85 (P=0.0001).

DISCUSSION

In women with severe preeclampsia shorter postpartum magnesium sulphate therapy was associated with lesser doses and duration of drug exposure with clinical outcomes were comparable to the control group who received 24 hour postpartum magnesium sulphate therapy.

The shorter duration postpartum magnesium sulphate therapy was found to be effective in this study group although the study did not have sufficient power to evaluate frequency of eclampsia. To evaluate the frequency of eclampsia in cases of preeclampsia treated with magnesium sulphate therapy will require a larger sample size which would require multicentric larger RCTs.

There are few studies found in the literature who has compared shorter duration of 6-12 hour postpartum magnesium sulphate therapy versus 24hour postpartum therapy in mild preeclampsia cases with almost equal efficacy.[9,10] In the present study we had taken all cases of severe preeclampsia with similar results as other studies. One RCT used the evaluation of urine output as the criterion for stopping magnesium sulphate postpartum in women with severe preeclampsia which was achieved at mean duration of 8.5±8 hours and they reported similar result as the present study. [7]In the present study none of the subjects in the study group required reinitiation of magnesium sulphate therapy after 4 hours. These observations indicate that the postpartum therapy with magnesium sulphate can be safely reduced from 24 hours to shorter duration of therapeutic anticonvulsant effect for 4 to 8 hours postpartum.

In the present study the mean duration of hospital stay after delivery was similar in both the groups. This suggest that the patients in the study group did not require monitoring in ward for significantly more hours than those who were in control group and patients in both group were stabilized in nearly same time.

The conclusion from this study is to encourage the use of short duration postpartum magnesium sulphate therapy with close monitoring upto 24 hours postpartum to avoid side effects and easy administration and monitoring in a busy labor room like ours. The shorter postpartum administration of magnesium sulphate also has the advantage of early ambulation, early removal of urinary catheter and early resumption of nursing of baby and other daily activities with lesser risk of magnesium toxicity.

It is our opinion that the use of short duration postpartum magnesium sulphate therapy for 4 hours instead of 24 hours, with maternal monitoring of vital signs and the symptoms and signs of imminent eclampsia every hour till 24 hour postpartum and reinitiating magnesium sulphate for 24 hours only when required is more appropriate and justifiable.

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